American Heart Journal

An international publication for the study of the circulation

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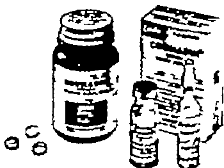
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American Heart Journal

January, 1961 Volume 61 Number 1

Editorial

Negative (gas) contrast angiocardiography

Thomas M. Durant, M.D.
Philadelphia, Pa.

Venous angiocardiography using opaque contrast solutions (positive contrast) has been established as a valuable adjunct in cardiac diagnosis ever since the original studies by Castellanos and co-workers.[1] Most of the recent advances in this technique have been improvements in the solutions used or in the roentgen recording, including biplane stereoscopic visualization and high-speed cineradiography. A new technique developed recently, however, makes use of a gas (negative contrast) medium or a combination of gas and an opaque medium (double contrast angiocardiography). This method, not designed by any means to replace older techniques, has been found nevertheless to have an important place in diagnosis, particularly in pericardial disease. Experimental work indicates furthermore that the sphere of clinical usefulness may be considerably extended in the not too distant future.

That a gas may be safely used as a contrast medium within the circulation will come as a surprise to many physicians who are well aware of the potential dangers of air embolism. It is indeed true that air, oxygen, or nitrogen may produce serious circulatory arrest and death when admitted inadvertently to vascular channels. Other gases, notably carbon dioxide and nitrous oxide, however, are well tolerated in large amounts without serious effects. The important difference between the former and latter as far as embolism is concerned is one of solubility. Carbon dioxide, for example, is at least twenty times as soluble in serum at 38.0°C. as is air or oxygen. This high solubility is responsible for the very rapid disappearance of bubbles from the circulation after injection and is no doubt responsible for the excellent no-fatality record of the Rubin test for tubal insufflation in gynecologic examinations in which carbon dioxide is the gas routinely used. Teschendorf[2] as early as 1951 had recognized the solubility factor and had recommended the use of either nitrous oxide or carbon dioxide for injections into the body cavity in order to avoid the danger of gas embolism.

During 1953-1954, while investigating roentgenologically in animals the mechanisms involved in circulatory arrest associated with intravenous injections of air, we were impressed by the excellent visualization of intracardiac structures provided by air.[3] Realizing that if such visualization could be safely achieved a valuable diagnostic technique would become available, we studied in dogs the effects of injecting 7.5 c.c. of carbon dioxide per kilogram of body weight (a) intravenously, (b) into the left heart, and (c) into the peripheral end of the ligated carotid artery.[4] The consequent cardiovascular, respiratory, and che-

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changes were minimal and lasted only seconds with any of these injections. By means of cinefluorographic technique the cardiac chambers, papillary muscles, valves, and great vessels were well visualized, and movements of the valve leaflets could be seen readily.

The first intravenous injections of carbon dioxide into human beings for the purpose of roentgen study were in anencephalic infants.[4] The dose was the same as that which had been used in animals (7.5 c.c. per kilogram). Brief respiratory disturbances were observed, as might be expected, but the injections were otherwise well tolerated. Excellent visualization of right heart structure and of the tricuspid ring were obtained roentgenologically. Since these original injections into human beings, approximately 80 adults have received doses of 50 to 100 c.c. intravenously at Temple University Medical Center. By comparison of body weight this dose is only approximately one fifth of that given to dogs in our experiments or to the two infants, and yet it has served well the purpose for which it was intended. It has not been used as yet for the [demon]stration of diseased valves, but the normal pulmonary valve has been well shown with doses of 100 c.c. One patient who had pulmonary emphysema with respiratory insufficiency received 50 c.c. without untoward effects.

The technique used routinely by Dr. Barbara Carter in our Roentgenology Department consists first in the establishment of a continuous intravenous drip via a three-way stopcock and a 20-gauge needle percutaneously in the left medial antecubital vein. For the demonstration of pericardial disease the patient is placed in the left lateral position so that the gas bubble during its brief sojourn within the heart (approximately 15 seconds) will be in a superior location adjacent to the endocardial surface of the right atrium and ventricle. The right lateral recumbent position is selected if visualization of the pulmonary valve is desired. Pure carbon dioxide is then thoroughly flushed several times through a 100-c.c. syringe, also via a three-way stopcock. This flushing may not be essential since, without it, the amount of air contamination could not be more than minimal, but it was established as a routine procedure early in our studies and does keep the safety factor in mind. It is important to emphasize that pure carbon dioxide is not the anesthetic mixture which contains only 10 per cent of this gas and which would be very dangerous. When these procedures have been performed, 50 to 100 c.c. of the pure carbon dioxide gas are injected rapidly into the vein via the stopcock of the intravenous apparatus. A roentgen exposure of the right heart border (factors: 85-100 kv., 400 Ma., 1/60 second) is made immediately after the injection and is followed as rapidly as possible by a second exposure. The films are examined while wet, and the study is repeated if necessary. Cinefluorography may be used to follow continuously the movements of the right atrial wall, but this is not essential if not available, since much important information can be obtained without it. In patients who have a very much elevated venous pressure, 100 c.c. of gas are usually required since smaller amounts are likely to be trapped in the superior cava until solution occurs. When the study has been completed, the patient is kept in the left lateral position for a period of 10 minutes or is turned into this position if the right lateral position was used for visualization of the pulmonary valve. This is another precaution which is probably not essential, but has been maintained as a routine procedure in order to avoid possible embolic effects.

The right heart wall (right atrium, pericardium, and pleura) normally measures 2 to 4 mm. in thickness and is convex laterally. When a pericardial effusion is present it appears as added soft tissue density between the bubble of carbon dioxide in the right atrium and the air-containing lung, thus increasing the thickness of the right heart border. In those patients who have a right-sided pleural effusion, the fluid within the pleura must be completely aspirated before the technique for pericardial visualization is used. It should be recognized that thickening of the mediastinal pleura or a mediastinal collection of fluid could appear as a pericardial abnormality, but such situations are infrequent in occurrence. Occasionally gas in the right ventricle may appear to be in the right atrium, especially in a rotated heart, thus simulating an effusion in the pericar

dium A soft tissue density along the caudal portion of the right heart border due to a pericardial pad of fat or to the inferior vena cava must not be confused When constrictive pericardial disease involves the right wall of the heart there will be straightening or angulation and rigidity of the atrial border Cineradiographic studies are particularly useful in the accurate evaluation of such alterations Since pericardial disease both effusive and constrictive is so often difficult to diagnose by clinical and routine roentgen methods[7] the additional information obtained by negative contrast study is often of vital importance

In our experience the advantages of gas over opaque contrast angiocardiography are (1) Pure carbon dioxide is safe there is no danger of sensitivity as with the various iodine-containing solutions now in use (2) A venous cut-down is not necessary (3) Carbon dioxide is not irritating to the vein (4) No elaborate equipment is needed (5) The gas is well tolerated and may be used in severely ill patients (6) Repetition is possible without danger of excessive roentgen exposure (7) There is no streaming due to poor mixing as may occur with opaque media It might be worthy of emphasis that the technique is one which may be used in small hospitals which do not have the usual angiocardiographic equipment

The advantages on the other hand of opaque over gas contrast angiocardiography are (1) A more extensive evaluation of the morphology and physiology of underlying heart disease is possible by the former technique (2) Effusions loculated along the left heart border anteriorly or posteriorly cannot be detected with gas in the right atrium but may be discerned with opaque contrast in other chambers (3) Overlying structures which might be confused with thickening of the right atrial wall may be better delineated with opaque material

It is quite possible that with further investigation the present disadvantages of gas contrast study may be overcome and it is particularly likely that other advantages may be found This is especially true of the demonstration of interatrial septal defects Quite generally it is agreed that angiocardiography with opaque medium is largely unsuccessful in the diagnosis of this congenital lesion Gas contrast and double contrast techniques on the other hand have readily demonstrated a surgically induced defect in dogs[8 9] In these studies the carbon dioxide passed through the defect from right to left according to the principle of gas buoyancy When the double contrast technique was used by Martin and associates[9] with the animal in the prone position the opaque medium was seen to pass through the heart chambers and pulmonary vessels in a normal fashion whereas the gas dissociated from the dye mixed blood and traversed the defect to the left atrium The best results were obtained when the former medium was introduced slightly ahead of the carbon dioxide A few attempts to demonstrate interatrial septal defects with gas in the human subject have failed in our clinic but it is quite possible that relatively minor changes in technique especially with respect to the position of the patient will make possible an important advance in the diagnosis of this lesion

The demonstration of left heart lesions by carbon dioxide in human beings remains for the future Our own hesitation in using such a study has been due to the fact that in animals injected with large amounts of the gas (7 5 c c directly into the left ventricle) a residual bubble may remain in the cavity of the heart for some minutes and this bubble has been found to contain nitrogen and oxygen The mixture is due to the diffusion of these other gases into the bubble of carbon dioxide according to the laws of gas equilibrium Theoretically this could lead to serious coronary embolism but there has been no evidence of this or of any serious effects in our animals If we can assure ourselves of the safety of this procedure it may be possible to demonstrate the movements of the aortic leaflets as we have been able to do cineradiographically in animal experiments In the latter we have been enabled to visualize also the coronary arteries very briefly and no electrocardiographic or other evidence of harmful effect has been demonstrated even under these circumstances On the other hand we have been unable to visualize successfully the abdominal aorta when injections were made into that vessel

Much remains to be done in the evaluation of this new technique with or without

double contrast in the visualization of various cardiac and vascular structures. Suffice it to say for the present, however, that a valuable method is now available for the diagnosis of many cases of pericardial disease in a safe and easy manner. We are gratified to note that other clinics in the United States and Germany[9-11] have confirmed our results and are using the method.

REFERENCES

1. Castellanos, A., Pereira, I., and Garcia, A.: Arch. Soc. Estud. Clin. Habana 31:523, 1937.
2. Durant, T. M., and Oppenheimer, M. J.: Med. Bull. Vet. Adm. MB-1, 16-57.
3. Teschendorf, W.: Acta radiol. 36:297, 1951.
4. Durant, T. M., Oppenheimer, M. J., Lynch, P. R., Ascanio, G., and Webber, D.: Am. J. M. Sc. 227:509, 1954.
5. Oppenheimer, M. J., Durant, T. M., Stauffer, H. M., Stewart, G. H., Lynch, P. R., and Barrera, F.: Am. J. Physiol. 186:325, 1956.
6. Stauffer, H. M., Durant, T. M., and Oppenheimer, M. J.: Radiology 66:686, 1956.
7. Durant, T. M.: Mod. Concepts Cardiovas. Dis. 27:455, 1958.
8. Winters, W., Wilson, M., Chungcharoen, D., Stauffer, H. M., Durant, T. M., and Oppenheimer, M. J.: Am. J. Physiol. 193:579, 1958.
9. Martin, J. F., Meredith, J. R., and Johnston, F. R.: Radiology 4:917, 1960.
10. Grosse-Brockhoff, F., Koch, D., Logen, F., et al.: Fortschr. Geb. Rontgenstrahlen 86:785, 1957.
11. Hoeffken, W.: Fortschr. Geb. Rontgenstrahlen 91:1, 1959.

Clinical communications

Tolazoline hydrochloride (Priscoline)
An effective pulmonary vasodilator

Robert F. Grover, M.D., Ph.D.
John T. Reeves, M.D.
S. Gilbert Blount, Jr., M.D.
Denver, Colo.

In the reduction of an elevated pulmonary vascular resistance, tolazoline hydrochloride has been reported to be effective by Dresdale and associates.[1] Gardiner, Braun and associates,[2] and Wood[3] but[4] found it to be of limited value, and Rudolph and associates[5] concluded that tolazoline was not an effective drug in this respect. These divergent impressions are probably a consequence of differences in the pulmonary vascular condition of the patients being studied, as well as of variations in the technique of administering tolazoline. It will be demonstrated in this report that when tolazoline is administered in an effective manner to carefully selected patients, a most impressive reduction in pulmonary arterial pressure and pulmonary vascular resistance can be produced.[7] The circulatory effects of tolazoline in normal individuals when it is administered by this same technique will also be considered.

Materials and methods

Eight children with isolated ventricular septal defects, 6 of whom were less than 30 months of age, were selected to illustrate the pulmonary vasodilator properties of tolazoline. Selection was based on the presence of a pulmonary vascular resistance which was at least twice normal, and the reduction of this resistance to normal after tolazoline.

Tolazoline was administered in the same manner to 11 normal subjects who ranged in age from 6 to 45 years. Four had functional murmurs, 5 had minimal tuberculosis, 1 had a cardiac neurosis, and 1 was an ambulatory inpatient with questionable epilepsy. Clinical and laboratory examinations, including cardiac catheterization, indicated that each of these subjects was suitable for this investigation.

Catheterization of the right heart was performed under sedation with secobarbital in all cases, supplemented with meperidine in the young children. The brachial or femoral artery adjacent to the catheterized vein was intubated with a fine polyethylene tube in every patient. Pressures were obtained by means of Statham transducers energized with a Hathaway carrier amplifier system and were recorded photographi

From the Cardiovascular Pulmonary Laboratory, Department of Medicine, University of Colorado School of Medicine, Denver, Colo.
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***Head, Division of Cardiology; Professor of Medicine; Director, Cardiovascular Pulmonary Laboratory, Department of Medicine, University of Colorado School of Medicine.

Table I Normal subjects Hemodynamic changes after tolazoline

Patient data				Pressure (mm Hg)		Heart rate	Saturation (% O₂)		Blood flow			Vascular resistance (dynes sec cm⁻⁵ M²)	
				PA	BA		PA	BA	A-V (ml/%)	O₂ (ml)	C O (L/min)	TPR	TSR
L W 22 2 kg	M	6 y 0 93 M	C	22/13(17)	100/69(78)	117	67 9	91 9	4 25	140	3 23	34	1 590
			T	19/10(11)		103	62 7	88 2	4 26	140	3 29	285	
J K 24 8 kg	M	7 yr 0 91 M	C	20/10(13)	85/61(71)	115	67 2	91 6	4 14	135	3 2	300	1 630
			T	19/12(15)	89/57(69)	115	59 1	94 1	5 11	190	3 52	320	1 175
J R 38 7 kg	M	12 yr 1 24 M	C	25/13(18)	95/65(79)	96	67 4	92 8	4 93	190	3 73	480	2 100
			T	17/9 (11)	91/55(73)	78	73 3	96 7	4 41	190	4 31	60	1 650
J V 43 6 kg	F	15 yr 1 36 M	C	19/12(15)	101/65(83)	95	[illegible] 9	96 6	4 37	210	4 81	310	1 875
			T	17/8 (11)	86/55(69)	67	64 6	96 1	5 90	210	3 62	330	2 075
L S 46 2 kg	F	16 y 1 47 M	C	29/14(19)	110/65 80)	62	77 1	99 3	4 17	175	4 20	530	2 240
			T	17/7 (12)	110/53(72)	90	79 8	97 0	3 26	205	6 79	235	1 345
B V 51 9 kg	F	21 yr 1 50 M	C	25/15(20)	108/59(75)	100	90 7	92 5	2 11	135	6 40	375	1 405
			T	24/9 (15)	118/60(9)	114	75 8	93 5	3 04	200	6 58	275	1 440
J O 58 5 kg	M	24 yr 1 68 M	C	16/8 (12)	118/68(85)	65	71 1	98 9	3 92	220	5 76	280	1 985
			T	20/8 (13)	117/65(82)	71	72 2	94 1	4 85	275	5 67	310	1 940
H P 55 2 kg	F	35 yr 1 51 M	C	21/9 (16)	96/56(69)	107	71 1	92 1	3 3	195	5 92	320	1 440
			T	18/8 (12)	106/60(75)	113	69 9	90 9	3 27	200	6 1	235	1 490
V C 62 3 kg	F	36 y 1 70 M	C	27/13(18)	130/66(91)	66	[illegible]0 5	92 1	3 80	200	5 26	475	2 350
			T	30/11(18)	129/65(83)	85	75 5	96 8	3 99	225	5 79	420	1 955
L V 54 0 kg	F	44 y 1 59 M	C	22/8 (14)	96/54(68)	97	78 8	98 9	3 55	155	4 37	420	1 980
			T	27/10(14)	86/50(62)	135	81 4	99 4	3 00	180	6 00	295	1 315
R M 93 5 kg	M	45 y 2 05 M	C	18/11(14)	112/76(98)	96	71 1	91 2	4 78	295	6 90	330	2 090
			T	21/17(15)	105/68(90)	93	71 6	85 3	2 91	265	9 11	270	1 440

Key to abbreviations C Control data T Values 10 minutes after tolazoline U der patient data Initials indicate individual subjects M Male F Female kg Weight in kilograms M Body surface area in square meters PA Pulmonary artery BA Brachial artery Pressures expressed as systolic/diastolic (mean) Heart rate in beats per minute A V Arteriovenous oxygen difference [illegible] Cubic centimeters of oxygen per 100 [illegible] of blood O₂ Oxygen uptake in [illegible] per minute C O Cardiac output TPR Total pulmonary resistance TSR Total systemic resistance

cally with a Hathaway oscillograph. Mean pressures were determined by planimetry. Samples of blood were analyzed for their oxygen content and capacity by the method of Van Slyke and Neill. Oxygen capacity of blood was determined on each sample of systemic arterial blood, i.e., for each determination of the cardiac output. Oxygen uptake was calculated by collecting expired air which was analyzed by the Scholander micromethod in duplicate. In small children it was not feasible to collect expired air. Hence oxygen uptake was estimated by means of a large body of data collected during a study of the metabolism of normal infants and children.* By means of height and weight, body surface area was determined from the charts of Sendroy and Cecchini. A linear relationship was found between the mean values for oxygen uptake and body surface area: 172 c.c. per minute per square meter for girls and 180 c.c. per minute per square meter for boys. It is of interest that Rudolph, using independent data, arrived at a figure of 180 c.c. per minute per square meter.

Blood flow was calculated by application of the classic Fick principle. When systemic arterial desaturation (below 90 per cent) was found in patients who had a ventricular septal defect, a right to left shunt was assumed to be present. To calculate pulmonary blood flow in those cases, a pulmonary venous saturation of 92 per cent was used.

Vascular resistance was calculated by dividing mean pressure by blood flow corrected for body size. This tends to remove the effect of body size on oxygen uptake, thereby giving similar normal resistance values for adults as well as for small children.[11] This is convenient and is helpful when the oxygen uptake is close to the basal metabolic rate, but the basic validity of such a correction remains to be established.

A complete set of control data was obtained with the subjects at rest. Tolazoline hydrochloride, 1 mg. per kilogram diluted to about 5 c.c. for convenience, was then injected over 45 seconds through the cardiac catheter directly into the main pulmonary artery. Even though the duration of the injection can be prolonged to 2 minutes, any other major variation in time or dosage should probably be avoided. Promptly after the injection is completed a cutaneous flush appears about the face and neck, and in blotchy areas over the rest of the body in some individuals. This is associated with a sense of warmth and usually disappears after about 5 minutes. Later there may be piloerection and a chilly sensation, and after 1 to 2 hours nausea with vomiting are not uncommon.

Systemic and pulmonary arterial pressures were recorded at minute intervals. After 10 minutes, allowing for stabilization of the circulation, cardiac output was again determined. In small children from whom expired air could not be collected, oxygen uptake was assumed to be unchanged from that of the control state. When a ventricular septal defect was present, the catheter was promptly withdrawn to the right atrium, and a sample of blood was obtained there also.

Results

A. The hemodynamic effects of tolazoline in normal individuals (See Table I.) The administration of a single moderate dose of tolazoline directly into the pulmonary artery in normal individuals had little effect on the mean pulmonary and systemic arterial pressures; it produced an average decrease of only 2 and 4 mm. Hg, respectively (Fig. 1,*A*). A mild tachycardia was usually observed (Fig. 1,*B*). The absence of systemic hypotension and the increase in heart rate have also been reported by other investigators.[12]

Tolazoline did not alter the cardiac output in the majority of these normal subjects (Fig. 2,*D*). Although the oxygen uptake tended to increase in these particular individuals (Fig. 2,*C*), statistical analysis of data from 35 subjects indicated a wide variation (S.D. ± 16 per cent) with no significant change (+8 per cent) in oxygen uptake after tolazoline. The change in the arteriovenous oxygen difference was also variable (Fig. 2,*A*). There was an increase in 4 individuals, a decrease in 4, and no change in 3. Since the pulmonary arterial saturation is related to the arteriovenous oxygen difference, the changes in this pa-

*The rationale for this assumption will be presented in the discussion.

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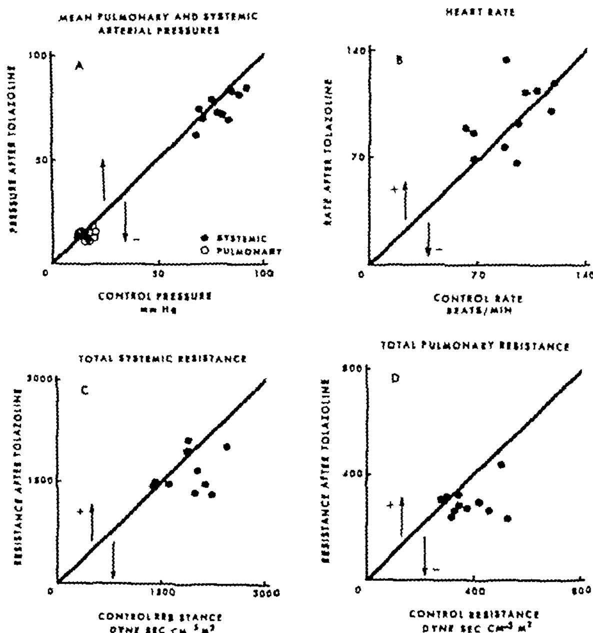


Fig 1 Effects of tolazoline on vascular resistance in 11 normal subjects Values for blood pressure heart rate and vascular resistance 10 minutes after injection of tolazoline are plotted against control values to indicate patterns of change

rameter after tolazoline were also variable (Fig 2 *B*) but in no case was there a marked increase in saturation This absence of consistent changes in either the arteriovenous oxygen difference or the oxygen uptake accounts for the usual lack of change in the cardiac output after tolazoline (Fig 2 *D*) Horwitz[14] using the ballistocardiograph came to the same conclusion

From these effects of tolazoline on pressure and flow the resultant changes in systemic and pulmonary vascular resistances are illustrated in *Fig* 1 *C* and *D* There was an obvious reduction in resistance only *in* those cases *in* which an increase in cardiac output occurred The effects of tolazoline on the pulmonary circulation of normal man have not been reported previously

B The hemodynamic effects of tolazoline in patients who have an increased pulmonary

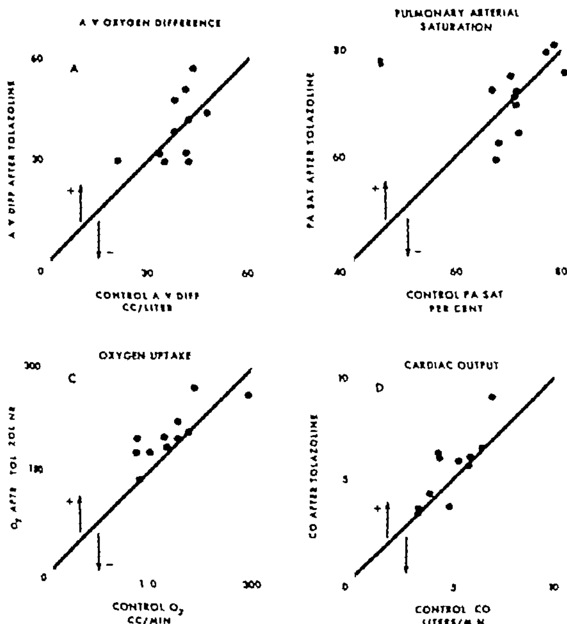


Fig 2 Effects of tolazoline on cardiac output calculated by the Fick equation in 11 normal subjects. Values 10 minutes after injection of tolazoline are plotted against control values to indicate patterns of change

vascular resistance associated with ventricular septal defect Marked pulmonary hypertension was present in every one of these 8 patients with the pulmonary arterial pressure approaching systemic levels in 6 (Table II) Tolazoline reduced the pulmonary arterial pressure impressively in each case An average reduction in mean pressure of 28 mm Hg (Fig 3) occurred promptly and was maintained for at least 20 minutes This reduction in pulmonary arterial pressure was often in the presence of an increase never a decrease in pulmonary blood flow due to an increase in shunting of blood from left to right through the ventricular septal defect

Concurrently tolazoline lowered the systemic arterial pressure but to a lesser degree the average reduction in mean pressure was only 9 mm Hg By contrast this reduction in systemic pressure was usually associated with a decrease in systemic

Table II. Patients with ventricular septal defect. Hemodynamic changes after tolazoline

Patient data				Pressure (mm. Hg) PA	BA	W	Saturation (% O₂) PA	BA	A-V O₂ difference (vol. %) Pul	Syst	O₂ ( )	Blood flow (L./min./M.²) Pul	Syst	Vascular resistance (dyne sec. cm.⁻⁵ M.²) PVR	SVR	PVR/SVR
M. I. 15 kg.	F	5 0.6 M.²	C	124/6 (51)	116/69(83)		65 5	81 5	4 72	4 60	143	3 03	3 11	1 325	1 340	0 99
			T	73/41(55)	95/57(71)		85 0	9 1	1 35	—	160	11 85		230		
B. K. 8 3 kg.	M	10 mo. 0.43 M.²	C	92/56(66)	97/67(80)	5	61 9	83 3	4 39†	5 0	77	1 75	1 52	1 295	1 505	0 ?
			T	56/12(30)	90 61(0)		73 5	96 1	3 05	5 33	77	2 50	1 14	470	1 6 0	0 5
M. O. 7 7 kg.	M	5 m 0.33 M.²	C	107/47(65)	82/52(66)		67 9	92 9	3 63	6 96	48	1 32	0 69	1 2 0	2 370	0 54
			T	72/ 7(40)	75/53(6)	—	75 5	96 2	42	5 70	45	1 95	0 99	500	630	0 19
K. I. 35 kg.	M	12 y 1 30 M.²	C	92/43(64)	95/62(73)	13	71 2	99 1	3 24	3 17	235	7 25	7 41	930	1 010	0 55
			T	67/35(45)	71/52(99)	—	52	91 5	? 16	4 97	235	10 55	4 73	430	1 295	0 33
J. J. 5 1 kg.	M	14 mo. 0.45 M.²	C	96/45(67)	110/61(79)		75 5	95 1	2 94	3 5?	81	2 75	2 12	975	1 340	0 65
			T	45/20(31)	102/5 (69)	—	75 1	55 1	2 64	5 63	81	3 07	1 44	9	1 725	0 25
L. M. 9 3 kg.	F	26 mo. 0.46 M.²	C	83/33(57)	116/62(83)	14	72 0	95 3	1 55	5 00	50	2 44	1 60	560	1 905	0 45
			T	43/25(32)	122/63(99)	—	74 0	96 9	2 75	5 70	90*	2 91	1 54	410	2 175	0 19
J. S. 11 3 kg.	F	30 mo. 0.55 M.²*	C	116/62(5)	115/78(93)	15	90 2	96 1	2 29	5 94	95*	4 15	1 5	825	2 565	0 32
			T	55/24(35)	113/59(79)	16	91 5	87 2	1 53	5 55	95	5 19	1 63	370	2 110	0 15
M. H. 9 8 kg.	F	20 mo. 0.48 M.²	C	0/36(47)	76/40(52)	9	0)	96 1	3 26	3 27	95*	? 5	2 51	715	85	0 91
			T	43/13(30)	61/40(48)	7	79 3	85 0	2 05	3 95	82	3 94	2 07	90	590	0 33

*Estimated.

†Patent ductus arteriosus ... per cent.

Abbreviations are the same as for Table I. C, Control data. T, Values 10 minutes after tolazoline. BA, Brachial artery or femoral artery. ... W, Wedge pressure ... Pul, Pulmonary. Syst, Systemic.

blood flow (Table II) Furthermore a clear separation of pulmonary from systemic arterial pressure was often achieved (Fig 4) whereas the two pressures were originally similar Likewise the ratio of pulmonary to systemic resistance which was originally high was reduced to normal after tolazoline (Table II) This illustrates the selective action of tolazoline on the pulmonary circulation in these patients

Pulmonary blood flow was considerably increased in 6 patients and modestly increased in the other 2 after tolazoline (Table II) These increases in flow accompanied increases in pulmonary arterial saturation resulting in a narrowing of the pulmonary arteriovenous oxygen differences

When a decrease in pressure was combined with an increase in flow a most impressive decrease in total pulmonary resistance was indicated (Fig 5) In every case the total pulmonary resistance fell within the normal range after tolazoline whereas the resistances were grossly elevated initially It follows that the decrease in resistance was related to the initial level of resistance the higher this resistance the greater the decrease after tolazoline in these particular patients Incidentally this same principle applied to the normal subjects of this report

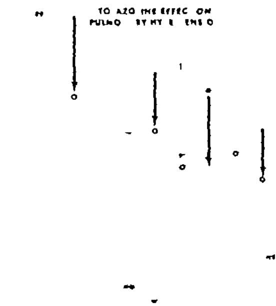


Fig 3 Reduction in pulmonary arterial pressures of 8 patients with ventricular septal defects and pulmonary hypertension who were given tolazoline

Discussion

A Pharmacology of tolazoline In reviewing the subject of adrenergic blockade Nickerson presented the various mechanisms by which tolazoline could produce vasodilatation Tolazoline will inhibit the pressor effects of epinephrine (adrenolytic action) as well as the vasoconstriction produced by stimulation of sympathetic nerves (sympatholytic action) In addition however tolazoline will produce vasodilatation in the sympathectomized limb Since this effect is not blocked by atropine it is probably not a cholinergic effect (even though tolazoline has other powerful parasympathomimetic actions) This then is a direct nonadrenergic relaxant action upon vascular smooth muscle which is a very important factor in the vasodilatation produced in man

Tolazoline produces the greatest vasodilatation in regions in which vasoconstriction is most marked [16] This effect can be largely confined to a single extremity by injecting tolazoline slowly into the artery which supplies that extremity [4] By analogy tolazoline should be most effective in relieving pulmonary vasoconstriction when injected directly into the pulmonary artery [3] These considerations underlie the method of administering tolazoline used in this investigation

When tolazoline is injected intravenously in normal man it does not produce generalized systemic vasodilatation Rather it produces a selective cutaneous dilatation with little effect upon the deeper resistance vessels of the systemic circulation This accounts for the cutaneous flush and initial sense of warmth observed in most subjects Subsequently there tends to be a loss of body heat and the increased metabolic rate (oxygen uptake) observed in some individuals is probably a compensatory mechanism which maintains body temperature The reported decrease in blood sugar [6,18] may be related to the increased metabolic rate or simply another manifestation of the adrenolytic action of tolazoline

Tolazoline increases the heart rate in man and in many other animals through direct stimulating action on the heart

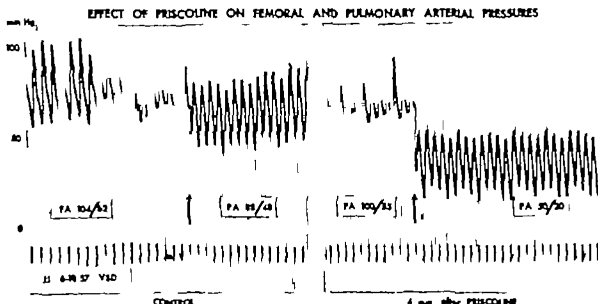


Fig. 4. Pressure tracings from Patient J. J. who had a ventricular septal defect and marked pulmonary hypertension. The single recording system was switched from the femoral artery to the pulmonary artery by turning a stopcock at the point indicated by the arrow. The two pressures which were originally of similar magnitude are clearly separated after tolazoline.

independent of the autonomic nervous system. Although this action does not increase the cardiac output in normal man receiving therapeutic doses of tolazoline (Fig. 2 D), larger doses in the isolated heart do increase cardiac output.[8]

Tolazoline rivals histamine as a powerful stimulant of the gastrointestinal tract in creasing salivary, gastric, and pancreatic secretions. This accounts for the delayed nausea and vomiting which may follow the administration of tolazoline. These are parasympathomimetic effects which can be blocked with atropine.

B. Pulmonary circulatory effects of tolazoline. Undisputable was the marked fall in pulmonary arterial pressure after the administration of tolazoline in the 8 patients of this report who had pulmonary hypertension and a ventricular septal defect (Fig. 3). The pulmonary arterial wedge pressure when obtained was normal and did not change (Table II). The normality of the wedge pressure in patients who have an uncomplicated ventricular septal defect has been well documented by Kjellberg.[1] Hence the observed decrease in pulmonary arterial pressure indicates a similar reduction in the pressure *gradient* across the pulmonary vascular bed.

An increase in pulmonary blood flow accompanied the fall in pulmonary arterial pressure. This flow was calculated from the oxygen uptake and the pulmonary venous and pulmonary arterial oxygen saturations. In certain cases only the pulmonary arterial oxygen content and saturation could be determined directly, and the other two factors had to be estimated on the basis of two assumptions: (1) the oxygen saturation of pulmonary venous blood was normal and remained constant, and (2) the oxygen uptake was not altered by tolazoline in those children in whom it could not be measured. Pulmonary venous blood was assumed to be 92 per cent saturated in those patients who had right to left shunts. This is a slightly lower figure than the normal arterial oxygen saturation of 94 per cent reported from this laboratory (elevation 5,300 feet).[27] Because of the possibility of hypoventilation in the sedated infants or of venous admixture[1,20,4] in these patients with an increased pulmonary blood flow, the value of 92 per cent was selected as a compromise. Calculations based on a higher saturation would give higher resistance values, but the difference would be consistent in a given individual. It is reasonable to assume that the pulmo-

nary venous saturation did not change after tolazoline since there was no consistent change in the arterial saturation of the 11 normal subjects

Although there is a tendency for the oxygen uptake to increase after tolazoline (Fig 2 C) this did not prove to be a statistically significant increase when a larger body of data was examined Hence when oxygen uptake had to be estimated it was assumed that the uptake remained unchanged after tolazoline This is a conservative assumption since an actual increase in oxygen uptake would further lower the pulmonary vascular resistance after tolazoline

The pulmonary arterial oxygen saturation increased in most cases and remained unchanged in the others after the administration of tolazoline When pulmonary blood flow is calculated from estimates based on the foregoing assumptions it follows that an increase in pulmonary arterial saturation due to tolazoline is in itself presumptive evidence of an increase in pulmonary blood flow

It has been established that the pressure gradient across the pulmonary vascular bed in these 8 patients was decreased after tolazoline in the face of a constant or increased pulmonary blood flow Consequently the calculated pulmonary vascular resistance was greatly decreased in every patient In all probability this means an increase in the total cross sectional area of the pulmonary vascular bed i e vasodilatation Since right atrial pressure did not change intrathoracic pressure was also presumably constant Furthermore the hemoglobin concentration was neither high nor variable in any of these patients so that changes in the viscosity of the blood are unlikely The decrease in pulmonary arterial pressure implies a decrease in the transmural pressure of the pulmonary arteries If the degree of vascular tone remained constant this would lead to a decrease in the caliber of the vessels Since the converse vasodilatation apparently occurred a marked decrease in pulmonary vascular tone after tolazoline is indicated

C Interpretation of results The 8 patients reported upon were carefully selected from a much larger series Two criteria were used in this selection first the total pulmonary

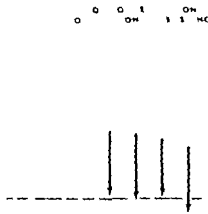


Fig 5 Reduction in elevated total pulmonary resistances of 8 patients with ventricular septal defects who were given tolazoline. The dashed line indicates the approximate upper limit of normal

resistance was initially high being at least twice normal and second the resistance was reduced to normal after tolazoline i e there was a gross decrease in resistance of more than 50 per cent in every patient Obviously then patients who exhibited the most noticeable response were deliberately selected to establish beyond question that under the proper circumstances tolazoline is a most effective pulmonary vasodilator

Tolazoline is just as effective in young children when the pulmonary vascular resistance is increased to a lesser degree than it was in the 8 patients reported upon here In older children tolazoline may not reduce an elevated resistance to normal even though there is a distinct pulmonary vascular response When a patient with congenital heart disease has had a very high pulmonary vascular resistance for years his pulmonary vascular bed usually becomes refractory to tolazoline

We believe that a vasodilator such as tolazoline will be most effective in those patients in whom the pulmonary vascular resistance is increased primarily as a consequence of generalized constriction of hypertrophied small muscular arteries When this smooth muscle is relaxed vasodilation can occur This responsive situatio

found most frequently in the first years of life as illustrated by the patients in this report When pulmonary hypertension has been present for years obliterative changes such as intimal proliferation and fibrosis thrombosis and atherosclerosis are found in the smaller pulmonary arteries When these lesions are widespread accounting for a large portion of the increased pulmonary vascular resistance a vasodilator could not be expected to lower the resistance appreciably However both the magnitude and the duration of the increased pulmonary vascular resistance are probably important in determining the age at which a given patient will lose his responsiveness to tolazoline

Tolazoline is potentially capable of reducing an elevated pulmonary vascular resistance whenever the increased resistance results from pulmonary vasoconstriction Although this report has been confined to patients who had isolated ventricular septal defects equally impressive results have also been obtained in patients who had other congenital cardiovascular defects When the increase in pulmonary vascular resistance is associated with hypoxia either acutely or e g in chronic pulmonary emphysema tolazoline has also been found to lower the resistance

Summary

Eight infants and young children who had ventricular septal defects and high pulmonary vascular resistances were carefully selected to illustrate the pulmonary vasodilator effects of tolazoline In each of these 8 patients tolazoline produced a marked reduction in pulmonary hypertension (average decrease 28 mm Hg) and an impressive decrease in pulmonary vascular resistance (over 50 per cent) to normal levels The effects of tolazoline on the cardiovascular dynamics of 11 normal subjects were also examined and found to be minimal When tolazoline is delivered directly into the pulmonary artery in a dose of 1 mg per kilogram over 45 seconds it is highly effective in relieving pulmonary vasoconstriction

REFERENCES

1 Dresdale D T Michtom R J nd Schultz M Recent studies in primary pulmonary hypertension including pharmacodynamic observations on pulmonary vascular resistance Bull New York Acad Med 30 195 1954
2 Gardiner J M The effect of Priscol n pulmonary hypertension Australasia Ann Med 3 159 1954
3 Braun K Izak G and Rosenberg S Z Pulmonary arterial pressure after Priscoline in mitral stenosis Brit Heart J 19 217 1957
4 Wood P Pulmonary hypertension with special reference to the vasoconstrictive factor Brit Heart J 20 557 1958
5 Yu P N Primary pulmonary hypertension report of six cases and review of literature Ann I t Med 49 1138 1958
6 Rudolph A M Paul M H Sommer L S nd Nadas A S Effects of tolazoline hydrochloride (Priscoline) on circulatory dynamics of patients with pulmonary hypertension Am Heart J 55 424 1958
7 Grover R F Bowen W A Jr and Blount S G Jr Pulmonary hypertension relieved by Priscoline in patients with congenital heart disease Clin Res 6 85 1958
8 Lee V A and Iliff A The energy metabolism of infants and young children during post prandial sleep Pediatrics 18 739 1956
9 Sendroy J Jr and Cecchini L P Determination of human body surface area from height and weight J Appl Physiol 7 1 1954
10 Barratt H C Cotton F S Laplace L B nd Scott J C The calculation of cardiac output and effective peripheral resistance from blood pressure measurements with an appendix on the size of the aorta ma Am J Physiol 115 312 1935
11 Hamilton W F Regulation of arterial pressure I Howell s Textbook of Physiology ed 15 Philadelphia 1947 W B Saunders Company p 711
12 Reeves J T Grover R F Filley G F and Blount S G Jr Cardiac output in normal resting man J Appl Physiol (In press)
13 Wakim H G Peters G A and Horton B T The effects of a new sympatholytic drug (Priscol) on the peripheral circulation in man J Lab & Clin Med 35 50 1950
14 Horwitz O Montgomery H Longaker E W and Sayen A Effect of vasodilator drugs and other procedure on digital cutaneous blood flow cardiac output blood pressure pulse rate body temperature and metabolic rat Am J M Sc 218 669 1949
15 Nickerson M The pharmacology of adrenergic blockade Pharmacol Rev 1 27 1949
16 Frandoni A C and Moser M Clinical appraisal of intra arterial Priscoline therapy n the management of peripheral arterial diseases Circulation 9 3 1954
17 Rottenstein H Horwitz O Montgomery H Sayen A nd Sterns L L The vasodilator effects of Priscoline in patients with ischemic extremities Am J M Sc 221 661 1951
18 Sherif M A F Razzak M A and Hasaballah A M Comparative study of some imidazoline derivatives nd dihydrogenated ergot alkaloid on blood sugar nd gastric

acidity Arch internat pharmacody 110 1 1957
19 James R G Certai metabolic effects of niacin and Priscoline Am J Physiol 1 146 1957
20 Ahlquist R P Huggins R A and Woodbury R A The pharmacology of benzyl imidazoline (Priscol) J Pharmacol & Exper Therap 89 271 1947
21 Kjellberg S R Mannheimer E Rudhe U and Jonsson B Diagnosis of Congenital Heart Disease ed 2 Chicago 1959 Year Book Publishers Inc p 377
22 Anderson L L Willcox M L Siltuna J and Blount S G Jr The pulmonary physiology of normal individuals living at an altitude of one mile J Clin Invest 32 490 1953
23 Ordway N K Studies in congenital cardiovascular disease IV Impaired pulmonary diffusion of oxygen in persons with left-to-right shunts Yale J Biol & Med 24 292 1952
24 Wood P Pulmonary hypertension Brit M Bull 8 348 1952

The management of resistant fluid retention states with intravenous L-arginine monohydrochloride in combination with mercurial diuretics

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In patients with resistant edema the production of hyperchloremic acidosis is an effective method for restoring responsiveness to mercurial diuretics[1] Calcium or ammonium chloride and more recently L lysine monohydrochloride have been used successfully for this purpose[1] The presence of nausea vomiting gastritis acute peptic ulcer[4] or an abnormal state of consciousness may make the oral use of these medications inadvisable or impossible In such instances a safe intravenous agent capable of producing adequate hyperchloremic acidosis would be of value

The effects of the calcium ion preclude the intravenous administration of large amounts of calcium chloride Intravenous ammonium chloride produces severe side effects[5] particularly in patients with Laennec s or cardiac cirrhosis[6,7] Lysine monohydrochloride is not yet available for parenteral administration On the basis of its role in the Krebs Henseleit urea cycle L arginine monohydrochloride has been administered intravenously in large doses to patients with liver disease[9,11] suggesting that this agent could be safely used in patients with resistant edema

It was therefore administered intravenously to a group of patients with mercurial resistant edema thus producing hyperchloremic acidosis and restoring mercurial responsiveness

Materials and methods

Five hospitalized patients with edema which was accompanied or unaccompanied by ascites due to either chronic congestive heart failure or Laennec s cirrhosis were selected for study The diagnosis was clearly established by history physical examination and appropriate clinical and laboratory tests Throughout the study the patients were treated with bed rest, 2 Gm salt diet fluid restriction to 1 200 to 1 500 c c per day and digitalis when

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indicated During the control period each patient received mercurial diuretics and 2 received a spirolactone but all failed to respond with significant loss of weight Distress attributed to marked retention of fluid made diuresis important or imperative The presence of nausea and vomiting acute gastritis or abnormal states of mentation precluded the use of oral agents capable of producing adequate hyperchloremic acidosis

A 500-c c intravenous infusion which contained 42 13 Gm of L arginine monohydrochloride* and provided 200 mEq of chloride ion was administered daily over a period of 2 to 4 hours When the desired effect had been produced (see below) daily intramuscular injections of meralluride (70 mg) administered as Mercuhydrin (2 ml) were begun continuing the daily administration of L arginine monohydrochloride in the dosage described Intake of fluids including the 500-c c infusion was limited to 1 200 to 1 500 c c a day

Daily body weight 24 hour urine volume and electrolyte concentrations as well as frequent determinations of plasma electrolytes and venous blood pH were obtained throughout the study Sodium and potassium were determined with a Baird atomic flame photometer using an internal lithium standard and chloride was determined by the method of Schales and Schales as modified by Summerson Carbon-dioxide combining power was measured with a Thomas–Van Slyke manometric apparatus and venous blood pH with a Cambridge research pH meter using a temperature correction of 0 0147 for each degree centigrade to correct to body temperature Blood urea nitrogen was measured by the Summerson modification of the Van Slyke and Cullen method

Results

Table I presents measurements of plasma and urine electrolytes and body weight in each patient during (1) the control period preceding the administration of L arginine monohydrochloride (2) production of hyperchloremic acidosis with L arginine monohydrochloride and (3) during daily mercurial injection with continued administration of L arginine monohydrochloride

Control period The lack of significant loss of weight during this period reflects the resistance of these patients to mercurials and to the other diuretics employed Concentrations of urinary sodium or chloride greater than 10 mEq per liter observed in several of the patients during this period represent in effect of the diuretics used these diuretics however were clinically ineffective The short control period in Patient W P was dictated by the urgent need for diuresis

Production of hyperchloremic acidosis with L-arginine monohydrochloride The daily parenteral administration of 42 13 Gm of L arginine monohydrochloride alone (200 mEq of chloride ion) for 1 to 3 days consistently produced a rise in the concentration of chloride in urine and plasma as well as a fall in carbon-dioxide combining power and in venous pH when the latter was determined Loss of weight did not occur during this period

On the basis of previous experience in this laboratory a significant increase in urinary chloride is one of the best indications that response to mercurial agents may ensue[3]

Mercurial administration after the production of hyperchloremic acidosis Daily mercurial injections and the continued daily administration of L arginine monohydrochloride after the production of hyperchloremic acidosis resulted in significant natriuresis diuresis and loss of weight in each patient The average weight lost per patient was 17 0 pounds or 3 3 pounds per day during this period

Plasma chloride carbon dioxide combining power and venous blood pH returned toward normal during the diuresis The administration of potassium chloride in amounts determined by the measured 24 hour excretion of potassium prevented the development of hypokalemia

In all but one patient was it possible to maintain the diuresis until adequate clinical response had been achieved In Patient J M the diuresis gradually diminished and it was necessary to discontinue the mercurial agent Subsequ production of hyperchloremic aci

*Kindly supplied by Cutter Laboratories Berkeley Calif

Table I. L-arginine monohydrochloride

Diagnosis	Cirrhosis of the liver			Congestive heart failure	
Patient	*J. M.*	*R. T.*	*W. P.*	*P. P.*	*E. K.*
Control Period					
Days	10	15	1	4	3
Weight change (lb.)	+2½	−3	—	+4½	−½
Urine sodium in mEq./L. (average)	3	13	15	3	12
Urine chloride in mEq./L. (average)	54	15	18	4	23
Plasma chloride in mEq./L. (average)	9	98	88	107	95
CO_2 combining power in mM/L. (average)	21.9	27.1	31.8	26.7	24.3
Venous blood pH (average)	7.34	7.44	7.46	——	7.44
Arginine Alone					
Days	1	2	2	1	3
Weight change (lb.)	0	0	0	0	−3
Urine sodium in mEq./L. (average)	1	5	31	3	5
Urine chloride in mEq./L. (average)	134	66	48	21	18
Urine chloride (mEq./L.)*	85 134	14 100	18 7	4 21	9 37
Plasma chloride in mEq./L. (average)	106	101	98	——	106

*The two values are the values obtained immediately prior to and after that period of treatment.

the same method then restored mercurial responsiveness.

Side effects. No side effects related to L-arginine monohydrochloride were encountered. Hyperpnea due to acidosis did not occur. Despite evidence of hepatic insufficiency in most of the patients studied, signs of hepatic encephalopathy did not develop in any instance during the study. Alterations in the hemogram or urinalysis attributable to the use of L-arginine monohydrochloride were not observed. Several of the patients developed a transient rise in blood urea nitrogen during treatment with L-arginine, but the blood urea nitrogen returned to pretreatment levels at the conclusion of therapy.

Discussion

The monohydrochloride salt of L-arginine has a molecular weight of 210 and therefore contains 4.76 mEq. of the acid amino-acid radical and of chloride ion per gram. Amounts of this agent similar to those used in this study have been rapidly administered parenterally to a large number of patients for the purpose of evaluating its efficacy in the management of hepatic encephalopathy.[11] Its effectiveness in this condition is controversial, but untoward effects in patients with hepatic insufficiency or in normal subjects have not been observed. Parenteral L-arginine monohydrochloride is therefore a particularly suitable agent for producing hyperchloremic acidosis in

Table I L arginine monohydrochloride—Cont d

Diagnosis	Cirrhosis of the liver						Congestive heart failure			
Patient	J M		R T		H P		P P		E K	
Arginine Alone—Cont d Plasma chloride (mEq /L)	99	106	98	107	88	98	—	—	88	116
CO₂ combining power (mM /L)	21.2	18.0	26.2	19.8	28.6	17.6	—	—	24.8	14.0
Venous blood pH	7.36	30	7.46	7.2*	7.46	7.32	—	—	7.44	7.25
Arginine With Mercuhydrin Day	7		7		6		3		3	
Weight change (lb)	−13		−17		−17		−16		−22	
Urine sodium in mEq /L (average)	33		55		73		74		67	
Urine chloride in mEq /L (average)	128		145		85		124		107	
Urine chloride (mEq /L)	134	94	100	131	57	92	21	115	32	103
Plasma chloride in mEq /L (average)	103		105		100		105		106	
Plasma chloride (mEq /L)	106	98	10	99	98	90	—	100	116	99
CO₂ combining power (mM /L)	18.0	18.5	19.8	24.6	17.6	23	—	24.3	14.0	20.2
Venous blood pH	7.30	7.39	7.28	7.48	7.32	7.38	—	7.34	7.25	7.40

*Th tw figs are th valu bt ed imm di tely pri to d afte th peri d f treatment

patients with retention of fluid secondary to hepatic cirrhosis or to congestive heart failure with its concomitant hepatic insufficiency [8,11]

The production of a hyperchloremic acidosis to induce mercurial responsiveness should be limited to those patients who do not respond to salt restriction bed rest digitalis when indicated oral diuretics and initial mercurial therapy When indicated oral agents may be successfully used to produce this metabolic state in most instances The use of parenteral L arginine monohydrochloride for this purpose should be restricted to patients who cannot take oral medications or in whom there is specific contraindication to the use of the available oral medications Therapy with this agent must be attended by careful clinical observation and laboratory control to avoid symptomatic metabolic acidosis and should be carried out only in hospitalized patients

Summary

The daily intravenous administration of a large dose of L arginine monohydrochloride is a safe and effective method of producing hyperchloremic acidosis and restoring responsiveness to mercurial diuretics in patients with refractory retention of fluid due to hepatic cirrhosis or congestive heart failure Results obtained with 5 patients thus treated and the advantages of this agent in certain clinical situations are discussed

REFERENCES

1 Rubin A L Thompson, H G J Braveman W S and Luckey E H The management of refractory edema in heart failure Ann Int Med 42 358 1955
2 Hollister J H Lubash G D Cohen B D Braveman, W S Rubin A L and Luckey E H Refractory edema treated with calcium chloride in combination with mercurial diuretics Am Heart J 56 629 1958
Rubin A L Spritz N Mead A W Herrmann R A Braveman W S and Luckey E H The use of L lysine monohydrochloride in combination with mercurial diuretics in the treatment of refractory fluid retention states Circulation 21 337 1960
4 Sackler A M and Sophian, L H The effects of the ingestion of amino acid on gastric secretion with particular reference to L lysine monohydrochloride Am J Clin Path 28 258 19
5 Stauffer J C and Scribner B H Ammonia intoxication during treatment of alkalosis in patient with normal liver function, Am J Med 23 990 1957
6 Phillips G B Schwartz R Gabuzda G J J and Davidson C S The syndrome of impending hepatic coma in patients with cirrhosis of the liver given certain nitrogenous substances New England J Med 247 239 1952
7 Bessman A N and Evans J M The blood ammonia in congestive heart failure Am Heart J 50 715 1955
8 Sievers M L and Vander J B Toxic effects of ammonium chloride in cardiac, renal and hepatic disease J.A.M.A. 161 410 1956
9 Farckas J F Tickun H E and Shea, J G Effects of L arginine on hepatic encephalopathy Am J M Sc 234 462 1957
10 Reynolds T B Redeker A G and Davis P A controlled study of the effects of L arginine on hepatic encephalopathy Am J Med 25 359 1958
11 Fahey J L Nathans D and Rairigh D Effect of L-arginine on elevated blood ammonia levels in man Am. J Med 23 860 1957
12 Kolet.ky S and Barnebee J H Cardiac or congestive cirrhosis pathologic and clinical aspects Am J M Sc 207 421 1944
13 Felder L Mund A and Parker J G Liver function tests in chronic congestive heart failure Circulation 2 286 1950
14 Evans J M Zimmerman, H J Wilmer J G Thomas L T and Ethridge C B Altered liver function of chronic congestive heart failure Am J Med 13 704 1952

Cardiac output in systemic arteriovenous fistulas complicated by heart failure

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Congestive heart failure is recognized as a complication of systemic arterio venous fistulas although it is not seen com monly in clinical practice The develop ment of this complication is related to the size and duration of the fistula Although many patients with simple systemic arteri ovenous fistulas have been studied sur prisingly few measurements of the cardiac output have been reported in these patients during heart failure The purpose of this re port is to present the cases of 3 patients with traumatic arteriovenous fistulas in whom the cardiac output was measured during a period of cardiac decompensation Certain hemodynamic considerations are discussed

Case reports

Ca 1 A 52 year-old retired railroad worker (#14 37 22) wa admitted on Nov 8 19 7 com plaining of shortness of breath hich had pers ted for 3 weeks H had noted the gradual ppearance of bilateral pedal edema and had gained 25 pound in weight Prior to admission he developed both dyspnea t rest nd orthopnea The patient de scribed gunshot ound in the left thigh from 25 caliber pistol 1924 I 1936 he developed weeping dermatitis on the lower part of his lef leg and chronic edema ppeared in this region H was ho pitalized on three occa ions for treatment of aricose eins and was retired from railroad service in 1954 because of this disabil ty Since then he ha been ble to do only part time labor

On phy ical examination the blood pressure was 120/80 mm Hg the pulse rate was 88 per minute and the eins the neck were distended There were scattered les over both lung bases The heart w enlarged but no significant murmurs were heard The liver was palpable 8 cm below the right costal margin A pulsatile mass which measured pproxi mately 8 by 8 cm was present in the left lower qua lrant of the abdomen I the lower third of the left thigh thrill was felt and a continuous murmur was heard There was moderat pitting edema of both legs more marked on the left The skin over the lower part of the left leg wa thickened and ndurated

Antecubital enous pressure was 260 mm of saline and the circulation time (arm to tongue Decholin) was 18 econds A roentgenogram of the che t howed marked cardiomegaly and an effusion in the right pleural cavity A electrocardiogram revealed normal sinus rhythm and left axis devia tion I Lead V the onset of the intrin icoid deflec tion was 0 05 second after the onset of entricular depolarization The T wa es were deeply inverted in Lead I V_L and V through V I Lead V the negativ T wave was 0 9 mv in amplitude

The patient was treated w th digitalis mercurial diuretics and diet restricted to 250 mg of sodium daily H lost 10 pounds in the first 10 days of ho pitalization Table I presents the results ob tained t cardiac catheterization on the sixth hos pital day On the twenty first hospital day repair as made of fistula which mea red 24 mm in diameter t the poi t of arteriovenous communica tion Recovery from the operation was uneventful The results of second cardiac catheterization performed 10 day after this operation are also presented in Table I Subsequently an aneurysm of the left iliac artery was excised and an end to-end

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anastomosis was performed The patient again recovered w thout incident Si months later he was admitted because of testinal obstruction At this time no evidence of congestiv heart failure was noted and roentgenogram of the chest did not reveal cardiomegal

COMMENTS This patient had a arteriovenous fistula for 33 years before congestiv heart failure occurred At the time of operation the fistula was large and was as ociated w th an aneurysm of the iliac artery Signs of regional enou insufficiency ppeared 12 years after the time of the original injury and led t his early retirement 3 years before operation The significance of the electrocardio graphic findings is difficult to assess since the possibil ty of coronary therosclerosis cannot be excluded completely These changes were not diagnostic of myocardial infarction however and are ascribed t chemia associated w th congestive heart failure The primary cause of his congestiv failure was almost certainly the increased work ocident to hi increased cardiac output The ex tremely long period of time between injury and the ppearance of heart failure has been described previously

Cas 2 A 57 year old man (#16 03 51) was adm tted on Dec 11 1958 because of progressive exertional dy pnea and orthopnea which had been present for 1 month Two years prior to admission h pri te physicia had treated him for congesti heart failure with digitalis The patient stated that he had been stabbed with knif n the right infracla icular region 35 years before Approxi ly 2 years after the time of injury he noted ted eins in the area of the sca At the same he al became w re of pulsating sensation n this region and felt that the circumference of his right arm became ncreased as compared to the left

On physical examination the patient appeared t be chronically ll The blood pre sure was 108/56 mm Hg in the right arm nd 112/50 mm Hg the left arm The pulse rate was 88 per min te The eins m h neck were distended A large pulsating mass was noted below the right clavicle A contin uous thrill was present in this region and the surrounding eins were noticeably dilated The circumference of his right arm was 29 cm whereas that of his left arm was 26 cm t the same level Scattered moist râles were heard over the lower part of the right lung field The maximal cardiac impul was in the left mid xillary line in the sixth i tercostal space The cardiac rhythm was regular A Grade 2 systolic murmur was heard over the base and was tran mitt d from the right infra cla icul region Digital compression below the right cla icle obliterated the thrill and resulted in a slow ng of the heart rat from 68 to 26 beats per minute The edge of the liver was palpable 6 cm below the right costal margin There was Grade 1 pitting edema m the pretibial area

The tal capacity was 1 2 liters The circulation time (rm t tongue Decholin) m the left arm was 40 second and the tecul tal venous pressure w 350 mm f saline Blood urea nitrogen was 23 mg per 100 ml Roentgenograms of the chest revealed mass cardiomegaly and engorgement of the pulmonary essel An electrocardiogram showed a normal sinus rhythm w th occasional premature ventricula contractions from multiple foci The onset of the intrinsicoid deflection was 0 06 second after the onset of ventricular depolariza tion in Lead V The T wa es were oelectric in the limb leads and negative in Lead V The data obtained at right heart catheterization on the eleventh ho pital day are shown in T ble I

Because t was believed that the patient was suffering from digitalis intoxication at the time of hi admission to the hospital digitalis was withheld Pota sium chloride was prescribed and he also received jections of mercurial diuretics During the first 7 day of hospitalization he lost 12 pounds weight but became lethargic I spite of attempts t improve his status by increasing his intak of fluid his blood urea n trogen rose to 60 mg per cent on the eleventh hospital day The initial efforts to improve his general condition w th medical management were nsucces ful The decision was made to proceed w th surgical intervention since this seemed to offer the only hope for surv val However because the blood pressure fell to 70/60 mm Hg on the morning on which the operation was scheduled postponement was necessary Ther py with norepinephrine and intra enous fluids was as ociated with a return to table blood pressure at 122/70 mm Hg Although he responded slightly to questioning he remained lethargic and expired the following day Autopsy was not performed

COMMENTS As in Case 1 this patient also had a extremely long period between the time of his original injury and the ppearance of congesti heart failure (33 years) The finding of cardiac output below normal is of importance in the presence of a large systemic arteriovenous fistula In this in stance systemic blood flow was severely reduced inasmuch as a large percentage of total flow was passing through the fistula U fort nately the fistula was situated beneath the clavicle where t could only be occluded by direct manual com pression I retrospect operation at the earliest possible moment after his admission might ha e been ad isable In any event the severely reduced systemic flow indicated an unusually high operativ risk

Case 3 A 56 year old attorney (#16 99 43) was admitted on Sept 18 1959 because of severe dyspnea H had been shot accide tally the right thigh while hunting 6 day before admission The patient was anemic the day aft injury nd was given 500 ml of whole blood t another hospital During the next few days he noticed dyspnea and experienced substernal discomfort In spite of dig talis therapy his dyspnea became more severe nd he was referred to th hospital for treatment

On physical examination the blood pressure as 130/80/70 mm Hg The pulse rate was 104 per minut The left border of cardiac dullness as 12 cm from the mid sternal line i the fifth left intercostal space The card ac rhythm was regular and the second heart sound was louder t the aortic than at the pulmonic val ular rea No m rmurs were present but protodiastolic gallop was heard at the cardiac pex The abdome protruded nd the edge of the liver extended 5 cm below the right costal margin There w a large hematoma over

Table 1 Cardiac output determinations

	Case 1		*Case 2*	*Case 3*	
	Preop	*Postop*	*Preop*	*Preop*	*Postop*
Right ventricular pressure (mm Hg)	32/22†	30/2	19‡	0/0	59/3
Oxygen consumption (ml /min)	293	217	174	296	215
Arteriovenous oxygen difference (ml /L)	31 1	49 1	45 1	23 7	32 3
Cardiac output (L /min)	9 42	4 42	3 88	12 49	6 65
Cardiac index (L /min /M²)	5 01	2 35	2 32	53	94

Pressure was measured [illegible] Statham strain gauge pressure transducer Gas samples were analyzed with [illegible] Beckman Model C oxygen analyzer Analyses of blood gas[illegible] were performed in duplicate by the method of D D Van Slyke and J M Neill (J Biol Chem 61 523 573 1924)
†Pulmonary artery
‡Right atrial pressure [illegible] this patient [illegible] the catheter could not be introduced [illegible] the ventricle [illegible] samples of blood for analysis were [illegible] from the atrium

the upper right thigh anteriorly A continuous bruit was felt, and a continuous murmur was heard in this region Attempts to obliterate the bruit by pressure were unsuccessful

The antecubital venous pressure was 140 mm of saline Sustained pressure over the liver while the patient breathed quietly caused [illegible] increase to 260 mm of saline The circulation time was 18 second (arm to tongue Decholin) Hemoglobin was 8 6 Gm per cent Roentgenograms of the chest made at the time of admission revealed cardiac enlargement The right pulmonary artery was noticeably dilated near its origin The lung fields were clear An electrocardiogram revealed sinus tachycardia and complete right bundle branch block.

The patient was transfused with 3 units of packed red blood cells He experienced some relief of dyspnea. On the seventh hospital day a right heart catheterization was performed (see Table I) Operation [illegible] was postponed in order to permit resolution of the edema and hematoma around the site of the fistula The patient was readmitted 8 weeks later for surgical repair of the fistula During the interim he had lost 47 pounds in weight. At operation on Nov 18 1959 a fistula which measured 5 to 6 mm in diameter was found between the superficial femoral vein and a branch of the profunda femoris artery The fistula was divided The patient tolerated this procedure well and recovered without incident. Five days later the right heart catheterization was repeated (see Table I)

COMMENTS The occurrence of congestive heart failure in this patient shortly after the establishment of his arteriovenous fistula was apparently due to several causes The presence of anemia may have increased the demands for a sustained high cardiac output The finding of [illegible] dilated right pulmonary artery together with right bundle branch block on the electrocardiogram and right ventricular hypertension at cardiac catheterization indicated an abnormality of the pulmonary circulation This undoubtedly existed prior to the time of injury It was not associated with respiratory insufficiency of any degree and therefore may have represented primary pulmonary vascular disease of some type The patient adhered strictly to his low ca[illegible] diet during the period before operation and it was felt that this accounted for the major part of his loss of weight

Discussion

The low resistance to the flow of blood through an arteriovenous fistula is analogous to a short circuit in an electrical system The pressure in the proximal artery is the same as systemic arterial pressure but falls sharply in the fistula and in the proximal vein The murmur and thrill result from turbulence in the region of the fistula The maintenance of a high flow through the fistula becomes essential if the remainder of the circulatory system is to be perfused This bizarre pattern of flow regularly affects the vessels in the region of the fistula The proximal artery becomes enlarged and tortuous True aneurysmal dilatation is not uncommon and occurred in the present Case 1 The veins in the region of the fistula exhibit thickened walls with muscular hypertrophy and intimal sclerosis Burton[1] has pointed out that tension in the vascular wall is directly proportional to the radius of the vessel Inasmuch as the regional artery is regularly enlarged one wonders whether systemic arteriovenous fistulas once established do not gradually increase in size

Frank and co workers[2] found that experimental fistulas with a flow of less than 20 per cent of the control cardiac output did not compromise systemic flow
cardiac output [illegible] d[illegible] suff[illegible]
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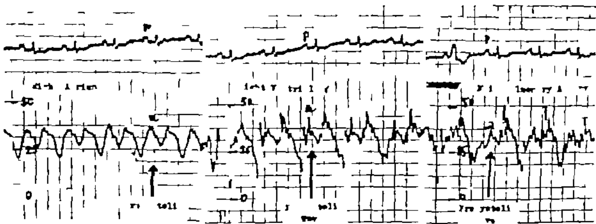


Fig 1 Case 1 Pressure curves from the right atrium right ventricle and main pulmonary artery in a case of fibroelastosis showing presystolic waves ( ) in the right ventricle and main pulmonary artery

of the cardiac shadow especially of the right atrium and right ventricle There was a slight dilatation of the pulmonary artery but no signs of pulmonary congestion

An electrocardiogram revealed sinus rhythm no alterations in conduction vertical electrical position and signs of right atrial and ventricular hypertrophy

The laboratory studies showed blood urea nitrogen 0 20 Gm per cent fasting blood glucose 1 05 Gm per cent Wassermann reaction negative sedimentation rate, Katz 15 erythrocyte count 4 200 000 and hemoglobin 1 5 Gm per cent leukocyte count 7 500 with 20 per cent lymphocytes 5 per cent monocytes 75 per cent neutrophils antistreptolysin-O titer 166 units per cubic centimeter The urinalysis was normal

Cardiac catheterization (Table I) performed on November 12 demonstrated severe hypertension in both venae cavae and in the right auricle In the right ventricle and pulmonary artery the systolic pressure was only slightly elevated whereas the right ventricular diastolic pressure was clearly elevated Pulmonary wedged pressure was markedly increased The cardiac output was decreased the pulmonary resistances were normal Analysis of the pulse contour (Fig 1) showed an M appearance in the right atrium In the right ventricle two tops were observed the first coincided with the presystolic wave of the right auricular tracing and the second was related to the ventricular contraction and was followed by a protodiastolic dip with late diastolic plateau In the main pulmonary artery the presystolic wave was again noted whereas the pulse tracing recorded from the right and left pulmonary branches was normal The pulmonary wedged pressure tracing did not show abnormalities

The possibility of either an anomaly of the tricuspid valve or constrictive pericarditis was considered to be consistent with the hemodynamic data but because the patient refused further investigations she was discharged on November 5

After she was discharged the exertional dyspnea increased and mild ankle edema was noted In March 1957 the patient entered a hospital outside of Italy Cardiac catheterization was repeated but pertinent data are not available however a diagnosis of constrictive pericarditis was made and the patient underwent cardiac operation During the thoracotomy no signs of pericardial involvement were observed Because of the appearance of the heart possible myocardial disease was suspected and right auricular biopsy was performed This showed an endocardial fibroelastosis The final diagnosis was primitive endocardial fibrosis The recovery was uneventful and the patient was discharged 1 month later The necessary course of the disease remained unchanged and 3 years later (February 1960) the patient was in rather poor condition

Case 2 T N 21 year-old man had been symptomless and active in his work as bricklayer until Feb 18 19 7 when he underwent an operation for acute appendicitis Five days later on February 23 the patient experienced a sudden aching pain in the precordium and left shoulder which radiated to the left arm he was without fever or dyspnea The blood pressure fell from 1 5/7 to 90/60 mm Hg An electrocardiogram (Fig) taken on the same day showed sinus rhythm normal P waves tall R waves in Leads D D₁ and V deep S waves in Lead V and an elevated R wave in Lead V monophasic current of injury was present from Lead V to Lead V During the following day while the monophasic wave gradually disappeared anterior ischemia and signs of diaphragmatic necrosis (deep Q waves in Lead D₃ D and aV and marked diminution of R in the same lead) were noted (Fig 3)

The diagnosis of postoperative myocardial infarction was made and the patient was treated with bed rest anticoagulant and strophantin His condition gradually improved and the electrocardiographic evolution was typical but at the same time progressively increasing tall T waves was observed in Leads D₃ and D and the precordial leads After this event of myocardial infarction the patient began to complain of exertional dyspnea

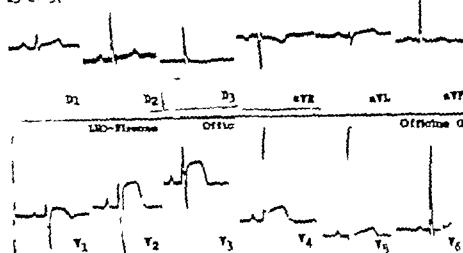


Fig 2 Case 2 Electrocardiogram (3 hours after the ppearance of precordial pain) monopha ic current of injury from Lead V to Lead V.

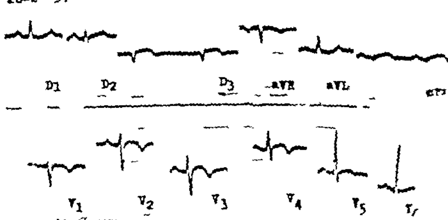


Fig 3 Case 2 Electrocardiogram (3 da after the ppearance of precor signs of diaphragmatic necros

and fatigue Because of these d turbances the patient was admitted to our Department on Sept 6 1957

At the time of admission physical examination howed him to be ell nourished man The blood pressure as 125 90 mm Hg and the pulse rate was 100 per minute The heart was clinically en larged the first heart sound as normal and t split and the second pulmonary sound en forced (F g 5) The liver was felt 2 f gerbreadth below the costal margin as tender and painles N other phy ical abnormalities ere detected The erythrocyte count was 3 080 000 and hemoglob was 16 Gm. per cent leukocyte count 6 500 th 33 per cent lymphocytes 2 per cent monocytes and 65 per cent neutrophils The urinalysis was

negativ Blood urea ar blood glucose was 0.81 g rate was normal negativ the units per cubic cen findings were normal

A chest film show ment was due mainl t tricle The pulmonary cardiogram (Fig 4) P as and a f QRS axis was in Leads D D small amplitude definite changes but the T was



Fig. 4. Case 2. Seven months after the appearance of a diaphragmatic necrosis a right auricular hypertrophy is noted (tall P wave in Leads D D and V).

and inverted, symmetrical and negative in the precordial leads.

Because the clinical and electrocardiographic data were considered to suggest pulmonary impairment associated with the past diaphragmatic myocardial infarction, catheterization of the heart was planned. On November 30 the patient was catheterized without complication and the pertinent data are summarized in Table I. There was a mild rise of pressure in the right ventricle and pulmonary artery, whereas the right auricular pressure was markedly enhanced and the pulmonary

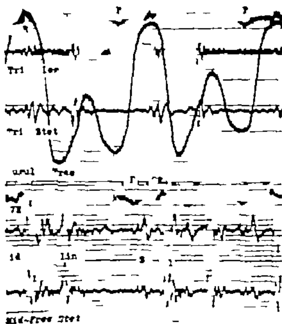


Fig. 5. Case 2. Phonocardiogram in the mid precordium showing a loud atrial sound (S) and a first sound (S_1) single, not duplicated. In the tricuspid area the first sound is also single and of low frequency and intensity. In the jugular tracing a giant a wave is noted.

wedged pressure was normal. In the right atrium a giant wave was present and was transmitted to the right ventricle and main pulmonary artery but not to the right and left branches; in the right ventricle the normal systolic wave was scarcely visible and in the pulmonary artery the dicrotic notch was not observed (Fig. 6).

The intracavitary electrocardiogram (Fig. 7) showed (a) in the main pulmonary artery giant negative P wave, (b) in the right ventricle a positive tall P wave and an rS complex of low amplitude with normal negative T wave, ( ) in the lower right atrium a giant positive P wave and in the mid upper right atrium giant negative P wave. Therefore the intracavitary electrocardiogram confirmed the existence of right atrial hypertrophy.

A possible diagnosis of unknown myocardial disease or cardiac tumor was considered to be consistent with the hemodynamic data and the patient was discharged on Feb. 15, 1958. He was followed up in the outpatient unit of our Department and for more than 15 months his general condition was unmodified.

On June 26, 1959, the patient was readmitted complaining of very severe exertional dyspnea which had been present for 3 days. His general condition was not changed but the cardiac shadow showed further augmentation. The blood pressure was 100/75 mm. Hg and the pulse rate was 110 per minute. The electrocardiogram was unaltered and laboratory tests were normal.

In order to establish the possibility of an operation by means of cardiac bypass, catheterization of the right heart was repeated (Fig. 8). In comparison with previous hemodynamic findings, the height of the wave was diminished in the right auricle, right ventricle, and main pulmonary artery; the systolic wave had almost completely disappeared from the right ventricle and pulmonary artery so that it was impossible to recognize the different cavities and levels of the right heart from the pulse contour. Moreover, there was equalization of pressure in the right auricle and ventricle and in the pulmonary artery.

A diagnosis of intracardiac fibroelastosis was suggested and the patient was discharged, being considered not suitable for open heart operation.

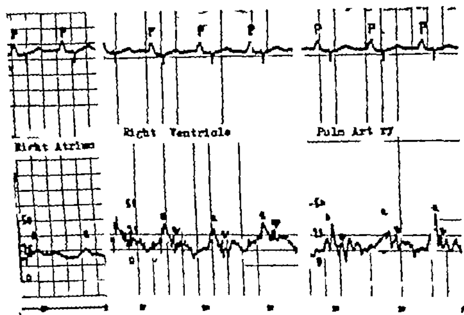


Fig 6 Case 2 Pressure curve from the right atrium right ventricle and main pulmonary artery in a case of infarction of the right ventricle Note the presence of an elevated presystolic wave (*a*) in the right ventricle and main pulmonary artery

On September 27 he was admitted in an extremely severe condition with very accentuated orthopnea cyanosis and somnolence Despite all therapy the patient died the following day

AUTOPSY Only the abnormalities pertinent to the heart will be reported in detail There was an engorgement of liver spleen and kidneys both lungs were ischemic no other major abnormalities were noted The heart weighed 300 grams The right ventricle was extremely dilated and its wall measured only 2 mm across The papillary muscles were thin white in color and almost completely transformed into fibrous tissue The right auricle was distended and greatly hypertrophied The left *atrium and left ventricle were normal The pulmonary* artery was normal but the aorta was hypoplastic Both coronary arteries arose from the aorta the left coronary artery was normal without signs of atheroma or sclerosis the right coronary artery was greatly hypoplastic but without obstructions

The microscopic appearance confirmed the replacement of the muscular tissue of the right ventricle with fibrotic tissue in which the muscle cells and vessels were practically absent. In the left ventricle no major microscopic abnormalities were detected except some small sclerotic areas

The final pathologic diagnosis was sclerosis of the right ventricle after a myocardial infarction without coronary obstruction

Discussion

In spite of some features in common in the intracardiac pulse contour these patients have presented a different clinical course and different pathologic lesions

The first patient had apparently a rather mild form of endocardial disease which involved the right auricle and the right ventricle but probably not the left heart This was demonstrated by the biopsy of the right auricular appendage and by the

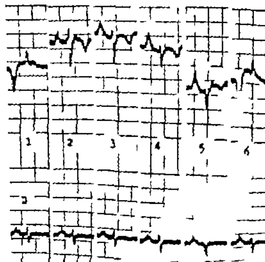


Fig 7 Case 2 1 intracavitary ECG obtained from 1 main pulmonary artery 2 outflow tract of the right ventricle 3 mid-apex right ventricle 4 ventricle below tricuspid valve 5 ... atrium 6 upper right atrium.



Fig. 8. Case 2. Pressure curve from the right atrium, right ventricle, and main pulmonary artery recorded months prior to the death of the patient. Note the presence of a prominent presystolic wave (a) in the right ventricle and main pulmonary artery with equalization of pressure in all the cavities.

presence of a clearly visible "a" wave in the right ventricle and in the main pulmonary artery, while the pulmonary wedged pressure was normal and no transmission of auricular waves to the brachial artery was present. Three years after the second hemodynamic study and the surgical exploration of the heart, no definite changes had occurred, and the patient presented a chronic disease with recurrent episodes of right heart failure rather well controlled by digitalis and diuretics.

In the second patient the disease began abruptly and ended 2½ years later with death from complete heart failure. The electrocardiogram had shown a typical picture of diaphragmatic myocardial infarction, in which it was possible to follow the normal electrocardiographic course: the recording of a current of injury, together with the rapid diminution of amplitude of the R wave in Lead D, D and aVF, and successively the appearance of a deep Q wave in the same leads, with disappearance of the monophasic wave and appearance of posterior ischemia. Later, while the signs of myocardial infarction persisted until the end, a pulmonary P wave developed, suggesting a chronic disease of the pulmonary artery and possible pulmonary hypertension. Actually, the first and second catheterization studies of the heart revealed the disappearance of an effective right ventricular contraction (the normal ventricular ejection wave had disappeared) and the maintenance of the pulmonary circulation by means of a strong auricular contraction (as evidenced by the recording of a giant "a" wave in the right ventricle and in the main pulmonary artery). The importance of right atrial contraction in supporting the pulmonary blood flow is also stressed by the coincidence of right heart failure with impairment of right auricular contractility. In effect, the second hemodynamic study, performed when the signs of right heart failure were present, revealed a decline of the presystolic wave, together with the reduction of cardiac output.

The pathologic examination showed an extensive replacement of muscular tissue by fibrotic tissue in the right ventricle, whereas the right auricular muscle was greatly hypertrophied, and the left heart cavities did not show signs of impairment. No coronary occlusion was detected, but there was a marked hypoplasia of the right coronary artery; this finding, together with the signs of myocardial infarction, supports the possibility of an acute myocardial infarction not dependent on a coronary occlusion, but probably related to the fall of blood pressure due to the shock of operation. The acute postoperative hypotension in the presence of a congenitally underdeveloped right coronary artery may have precipitated an acute coronary insufficiency due to functional vasospastic mechanism. The possibility of cardiac infarction in the absence of coronary obstruction as a consequence of a sudden fall of blood pressure is well known. Since the original paper of

Friedberg and Horn [9] myocardial infarctions in the absence of coronary occlusion have been found rarely (only 0 7 per cent in the gross anatomic material of Goder [9]). This points out the importance of an isolated sudden fall of blood pressure as the cause of coronary insufficiency.

Infarction of the right ventricle is exceedingly rare [11] Moreover it does not present distinctive electrocardiographic patterns [7,11] and is followed without exception by death in the first few days depending on the contemporary involvement of the left ventricle due to the lack of a particular distribution of coronary blood flow for each ventricle [12] To our knowledge no cases of isolated right ventricular infarction in human beings have been reported in the experimental field however the production of right ventricular massive infarction is not usually followed by death [13] and some authors affirm that the right ventricle is not essential in the performance of cardiac function at least for a few months.

In our case the electrocardiographic signs of right ventricular infarction were evident and were dependent on the fact that the inferior and anterior surfaces of the heart were formed by the right ventricle the replacement of muscular tissue by connective tissue was not followed by immediate death since the right auricle did maintain the pulmonary circulation. Possibly there was a congenital hypofunction of the right ventricle so that the complete loss of its contractility was not so severe as would have been that of a well functioning right ventricle. However the late appearance of signs of right atrial hypertrophy demonstrates that the right auricle had supplied the declining function of the right ventricle only after acute coronary insufficiency had developed.

As previously mentioned recording of auricular waves from the right ventricle has been observed by some authors. This has been noted occasionally in Ebstein's disease in the so-called atrioventricular common chamber (so-called ventricularization of right auricular pulse contour).

More recently Bayer and co-workers noted a similar pattern in the right ventricular chamber and in the pulmonary artery in a case of supposed endocardial fibroelastosis. These German authors suggest the possibility that the right atrium participates actively in the dynamics of the heart as a second ventricle and this would be demonstrated also by the equalization of pressure in all cavities.

A giant a wave in the right atrium as well as the equalization of the mean pressure can be recorded in cases of con

Table I Catheterization findings

	A L 26 year old woman (Cath N 4)		*T V 30 year old man* (Cath N 541)		(Cath No 907)	
	Intracardiac pressures (mm Hg)	*Oxygen content* (vol %)	*Intracardiac pressures* (mm Hg)	*Oxygen content* (vol %)	*Intracardiac pressures* (mm Hg)	*Oxygen content* (vol %)
R A	35 19 25	10 78	25 1 20	12 90	18 11 14	—
R V	42 15 —	10 76	30 10 —	12 95	20 9 —	—
P A	42 16 26	10 81	30 10 18	13 07	18 11 15	14 67
P W P	— — 17	—	— — 13	—	— — 10	—
B A	125 85 —	16 5	120 7 —	18 50	135 80 —	21 89
O_2 capacity	18 4 vol %		20 4 vol %		24 75 vol %	
O_2 saturation	89 %		91 %		88 %	
O_2 consumption	160 /m		190 /min		185 min	
Cardiac output	2 7 L/ min		3 5 L /min		2 6 L min	
Cardiac index	1 6 L /min M		1 9 L /min /M		1 4 L min M	
P T R	770 dynes/sec /cm		39 dynes/sec /cm		480 dynes/sec cm	
P.A.R	266 dynes/sec /cm.		110 dynes/sec /cm		160 dynes	

strictive pericarditis or in other adiastolic states[6] However in not one of the aforementioned disease states has a presystolic wave been observed outside the right auricle

In our cases an auricularization of the right ventricular pulse was present yet its significance is different in the two cases In the first patient the presystolic wave was followed by a normal systolic wave which was also recorded in the pulmonary artery thus demonstrating that the right ventricle had partially maintained its propelling force and contributed to the pulmonary circulation In the second patient the first catheterization showed a very tall presystolic wave in the right ventricle, and only some small deflections in coincidence with the ventricular contraction The pulmonary valves were opened only by the atrial contraction When the patient was recatheterized 3 months prior to his death the efficiency of the right ventricle was found to be further reduced since the atrial systolic wave was diminished in amplitude the systolic remnants of ventricular contraction were no longer visible and the cardiac output was greatly decreased This clearly demonstrates that the right atrium alone maintained the pulmonary output

It is interesting to observe that the presystolic wave was more elevated in the right ventricle and in the main pulmonary artery than in the right atrium This was due possibly to the loss of elastic properties of the right ventricle so that the ventricular wall which was inextensible behaved as a stiff pipe The loss of the normal distensibility of the right ventricle produced when the blood entered the cavity a diminished recoil of the ventricular wall which was responsible for the augmented intraventricular pressure The disappearance of the a wave in the left and right branches of the pulmonary artery can be explained on the basis of the maintenance of pulmonary recoil

Previous cases as well as our patient suggest the possibility that different pathologic and clinical entities can occasionally give similar hemodynamic pictures Right auricular waves from the right ventricular chamber and the main pulmonary artery can be recorded in instances of complete right ventricular disability which may or may not be compatible with life The possibility of a prolonged survival depends mostly on the pumping capacity of the right auricle and its failure has the significance of irreversible right heart failure

Summary

Two cases are presented which show particular hemodynamic patterns characterized by the recording of an auricular pressure curve from the right ventricle and the main pulmonary artery

Anatomic study proved the clear distinction between the two subjects In the first patient the biopsy of the right auricular appendage performed during the cardiac operation showed a diffuse endocardial fibroelastosis in the second patient at autopsy a massive fibrosis of the right ventricle dependent upon an infarction of the right ventricle was observed

Evidence is presented to support the view that the pulmonary blood flow was maintained by the contraction of the right atrium which was greatly hypertrophied whereas the right ventricle acted merely as a passive stiff chamber

The right heart insufficiency appeared when the right atrium failed to support the pulmonary circulation the congestive failure coincided with the failure of the right atrium

From the study of these cases the nonessentiality of the right ventricle in the pump mechanism of the heart previously observed in the experimental field seems to be demonstrated also in human beings

REFERENCES

1 Bakos A C P The question of the function of the right ventricular myocardium an experimental study Circulation 1 724 1950

2 Bayer O Breu J and Moeller P D Z Fibroelastosis endocardica unter besonderer Berücksichtigung der Diagnose intra vitam Arch Kreislaufforsch 28 217 1958

3 Bean W B Infarction of the heart clinical course and morphological findings Ann Int Med 12 71 1938

4 Broadbent J C Wood E H Burchell H B and Parker R L Ebstein malformation of the tricuspid valve report of 3 cases Proc Staff Meet Mayo Clin 28 79 1953

5 Condorelli L L infarto emorragico prestatico del cuore Commun Soc Med Chir Catania 10 13 1942

6. Dalla Volta S Battaglia G and Zerbini E Diagnosi differenziale emodinamica delle adiastolie Mal cardiovasc 1 ?/63 1960
7. Dressler W and Roesler H Variations in the deviation of S-T in [illegible] terior wall infarction Am Heart J 3 58 1948
8. Faralla A Sangiorgi M and Bompiani G D Cood xelli s prestatic infarction Cardiologia 33 769 1958
9. Friedberg C K and Horn H Acut myocardial infarction not due to coronary occlu ion J A M A 112 1675 1939
10. Goder G Der akute todliche Myokardinfarkt Ztschr Kreislaufforsch 49 105 1960
11. Van Lingen B McGregor M Kaye J Meyer M J Jacobs H B Brando J L Bothwell T H and Elliot G A Clinical and cardiac catheterization findings compatible with Ebstein anomaly of the tricuspid valv A report of tw cases Am Heart J 43 77 1952
12. Starr I Jeffers W H and Meade R H The absence of con picuous increments of enous pressure after severe damage t the right ventricle of the dog with a d scussion of the relation between clinical congestiv failure and heart disease Am Heart J 26 791 1943
13. Wade W G The pathogenesis of infarction of the right entricle Brit Heart J 21 545 1959
14. Wartman W B and Hellerstein H K The incidence of heart disease two thousand consecutive autopsies Ann I t Med 28 41 1948
15. Wolferth C C Bellet S Livesey M M and Murphy F D Negativ di placement of the S-T segment in the electrocardiogram and its relationship to positive displacement an experimental tud Am Heart J 29:220 1945

Correlation of clinical information in the standard 12 lead ECG and in a corrected orthogonal 3-lead ECG

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The extent to which 3 orthogonal electrocardiographic leads record all electrical information which is available from the body surface has been debated since the advent of vectorcardiography. Can the standard 12 lead electrocardiogram be replaced by 3 orthogonal leads without appreciable loss of clinical information? Problems related to such reduction in number of leads have been amply discussed previously. Recent attempts to automate ECG analysis by use of electronic computers have emphasized the necessity of a reduction of data and elimination of redundant information.[3] Reduction in the number of leads has become, therefore, a prime objective of electrocardiographic research. Before such a step can be recommended, however, conclusive evidence is required that no information of clinical significance is sacrificed by the use of fewer leads.

It has been suggested that recording preferentially from local portions of the heart by use of precordial leads may provide information not supplied by an orthogonal 3 lead system.[7] On the other hand, some proponents of orthogonal lead systems believe that practically all electrical information available from the body surface could be attributed to a single *fixed* point-like dipole equivalent.[8,1] This hypothesis has been questioned,[11,4] however, and no generally accepted concept on the physical characteristics of the heart as a generator of current exists at present.

Recent studies by Scher and associates[7] shed further light on the question of the minimum number of required leads. Using electronic computers, they investigated mathematically how many independent variables or factors (in linear combination) can account for a variety of surface leads. The number of independent variables equals the number of leads required. This study indicated that 3 leads were sufficient to record all electrical information from the body surface of normal subjects. The authors pointed out that the assumption of a dipole equivalent is not a necessary condition for the reduction of leads to 3.

Other approaches to the problem of determining whether 3 leads are adequate have consisted mainly in qualitative comparisons between vector loops and standard ECG leads.[19] Generally, good agreement between the two types of data has been

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found and the orthogonal leads were considered to be sufficient for a complete description of the body surface ECG. However the number of cases studied in this fashion has been relatively small.

A detailed comparison of the clinical information contained in the 12 lead ECG and 3 orthogonal scalar leads (Frank's system [4]) has been reported recently by Abildskov and associates in a series of 71 cases. A search for diagnostically significant patterns found in the standard leads was made in orthogonal 3 lead records. In almost 10 per cent of the cases such diagnostic features could not be recovered in the orthogonal leads. Patterns of lead from 3 directions were compared however with those from 12 directions. This discrepancy in the display of data obviously favors the standard leads by a ratio of 1 4. Information may have been contained in the 3 orthogonal leads but was not displayed in the familiar patterns of the standard ECG which were used as the only criteria for the comparison.

In order to circumvent such shortcomings a more refined approach to the same problem was used in the present study. A first comparison was made between the standard 12 lead ECG and 3 corrected orthogonal leads (Schmitt's SVEC III system [7]). Additionally in order to obtain a display of data in the orthogonal ECG which is comparable to that in the standard ECG a second correlation was made. The 3 basic orthogonal components were resolved [1-3] to obtain additional leads from directions generally assumed for the standard ECG. Resolved leads merely represent linear combinations of the 3 basic leads. Therefore they cannot possess any new information not contained in the basic components. In this fashion however a directly comparable display of data is obtained for both types of leads. The readings of the two sets of records were performed by independent interpreters in order to avoid any bias through knowledge of findings in a record to be compared. This blind feature of the study was an essential safeguard because it is common experience that one may read information into an electrocardiogram.

Correlations of the content of clinical information do not lead to a physical definition of the heart as a generator of current and are purely qualitative. The advantage of a clinical correlation however lies in its immediate applicability without the need for theoretical notions on the heart as a generator of current.

Materials and methods

A random selection of 261 patients who showed abnormal features in their electrocardiograms was used for the present study. The distribution of their ECG diagnoses is shown in Table I. In each of these cases a standard 12 lead electrocardiogram was taken together with a corrected orthogonal 3 lead electrocardiogram (Schmitt's SVEC III system [7]) including resolved leads from directions comparable to those of the standard leads. The design of the switching type of resolver used was described previously. An example for the method of arriving at resolved leads is shown in Fig 1. The directions of the resolved lead are indicated in Fig 2. They were designated according to their plane of projection. Resolved leads in the frontal plane which corresponded to the standard limb leads were called XY leads in the horizontal plane XZ leads and in the sagittal plane YZ leads. An angular scale with clockwise rotation from 0 to 360° was used for each plane. 0° was always to the right of the observer (Fig 2). Two leads in the horizontal plane (XZ 120 and 150) and 4 leads in the sagittal plane (YZ 30 60 300 and 330) have no counterpart in the standard ECG. Except in two cases indicated below they were not used for the correlation. A 4-channel direct

*Table I Distribution of electrocardiographic interpretations**

Left ventricular conduction defect	15
Right ventricular conduction defect	19
Intraventricular conduction defect type undetermined	1
Right ventricular hypertrophy	9
Left ventricular hypertrophy	89
Biventricular hypertrophy	8
Myocardial infarction	
1 Anterior and anteroseptal	37
2 Diaphragmatic and high posterior	4
3 Lateral	15
Non specif changes	50
	285

* [illegible] of 261 cases more th[illegible] ECG diagnoses. These ha[illegible] been i[illegible]cluded [illegible]

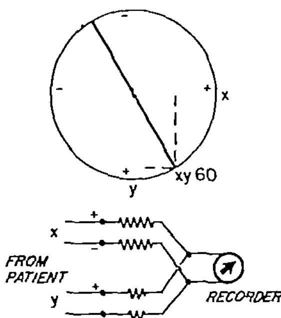


Fig. 1. Method for resolution of orthogonal leads. Lead XY 60 of the frontal plane (comparable in direction to standard lead II) is shown as example. In the upper diagram this lead is projected on orthogonal leads X and Y. Lead resolution consists of a linear combination of these two leads in proportions equal to the size of the projections. The lower diagram shows the attenuation of lead X and Y to the proportions indicated by the projections. The relatively smaller X value requires larger resistors for lead X but the larger Y value needs less attenuation. The proportions and required resistors are calculated according to: $XY = \pm X \cos \alpha \pm Y \sin \alpha$, where angle α indicates the direction of the desired lead.[10]

writing electrocardiograph* was used for all tracings using a paper speed of 50 mm. per second. The recording method for the SVEC III lead system has been reported previously.[11] Standard lead I and orthogonal lead X were used as time reference for the two sets of tracings, respectively.

The standard and orthogonal tracings were marked with a code number and then given to two independent readers for analysis and interpretation. Special emphasis was placed on minor details of the records, such as notching of QRS complexes, T and S-T changes. The abnormal features were listed by each reader, and finally an electrocardiographic interpretation was made. Discharge summaries with code numbers for each patient were also available to the interpreters. ECG findings listed in these summaries had been deleted.

*Poly Viso, Sanborn Company, Waltham, Mass.

The interpreter who read orthogonal records proceeded in the following fashion. At first he analyzed the 3 basic orthogonal leads only and listed his findings. Subsequently, he read the complete set of resolved leads in addition to the 3 basic leads. This was done in order to evaluate the influence of an additional display of data derived from resolved leads. At the end of the study, tracings and readings of both standard and orthogonal leads were compared and listed.

The interpretation of the records was based on a "pattern type" of analysis commonly used in clinical electrocardiography (Q wave measurements, incidence of abnormal QS or RSR' configuration in certain leads, etc.). The correlation, therefore, was essentially based on a pattern comparison. *Because of the large variability in direction* of effective lead axes of conventional leads, a lead by lead correlation between the two sets of compared tracings could not be expected. The search for corresponding patterns, therefore, was always extended over a certain angular range of adjacent leads.

Results

1. Comparison of the 12 lead standard ECG with the 3 lead orthogonal ECG. In 242 out of 261 patients the features which led to electrocardiographic diagnosis in the standard 12 lead ECG could be completely *recovered from the 3 orthogonal leads.* This represents 92.7 per cent of the total group.

Several types of electrocardiographic abnormalities recognized in the standard leads could not be found in 19 orthogonal 3 lead records. In 8 of these cases with lack of clinical information in orthogonal leads small R waves with little or no R wave progression was found in right precordial leads (V_1 to V_3 or V_4). This sequence could not be recognized in the sagittal lead Z. Such findings are frequently labeled as "compatible with loss of anteroseptal electrical forces," although they may also be found in patients with left ventricular hypertrophy, left ventricular conduction defects, and occasionally in normal individuals. *Since this feature was not clearly* recognized in the orthogonal leads, these 8 cases were counted as deficient in clinical information.

In 4 other cases an RSR' pattern in

standard lead V_1 without counterpart in the sagittal lead Z was found. Abnormal Q waves in lead aVL (0.04 sec duration and amplitude of 0.2 mV) were found in 2 additional cases. The closest counterpart of this lead, the horizontal orthogonal lead X, failed to show any Q wave abnormality. A similar discrepancy was seen in 2 cases with QS waves in leads III and aVF without such finding in the vertical lead Y. A further case showed a QS pattern in leads V_1 and V_2 but the sagittal lead Z was of the

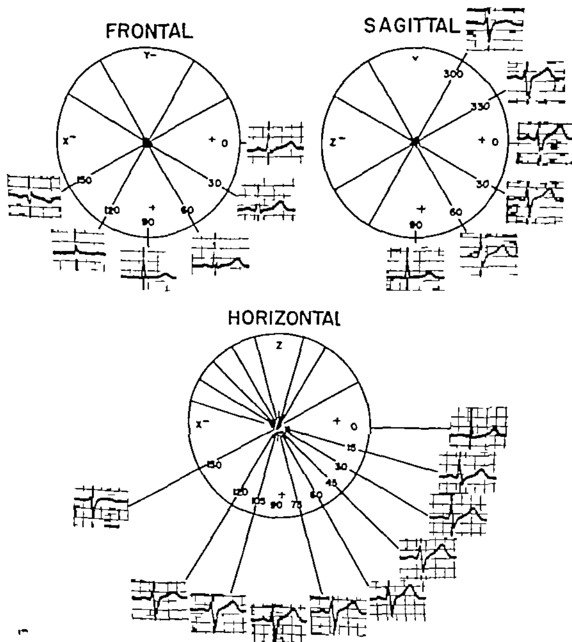


Fig. 2. Resolved orthogonal leads in the frontal (XY), horizontal (XZ) and right sagittal (YZ) planes. The choice of leads in the frontal and horizontal planes was based on the approximate directions of conventional leads. The resolved leads in the sagittal plane and leads XZ 120 and 150 have no counterpart in the 12 lead ECG and [illegible] are not used for the correlation. Broken vertical lines indicate the peak of the R wave [illegible] in lead X, which was taken as time reference lead. (From Pipberger and Wood[35] by permission of the American Heart Association, Inc.)

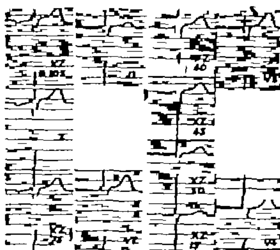


Fig 3 Standard leads V to V are of the rS type and do not show any R wave progression A sudden transition from rS to RS is seen in V The lack of R wave progression is also seen in the XZ leads from 105 to 30 with an analogous transition from rS to RS in XZ 15 The orthogonal lead Z of this record was found to be abnormal with an R/S ratio of less than 0 10 The broken vertical lines in this and the following figures indicate the R wave peaks in lead V and I which were taken as time reference leads for the two sets of tracings respectively

rS type Another patient s record had QS waves in leads V to V Neither the horizontal lead X nor the sagittal lead Z were found to be abnormal in configuration A last case showed a so-called isolated T wave negativity in leads V₃ and V i e T waves to the right and left of these leads were found to be upright The orthogonal ECG showed mainly negative T waves both in leads X and Z The T wave abnormality therefore was not recognized in the orthogonal leads

After the correlation of patterns the cases with deficiencies in clinical information in orthogonal leads were singled out for further analysis The preliminary normal standards developed in this laboratory for Schmitt s SVEC III lead system[4] were applied to these cases and deviations from normal ranges were noted In 5 out of 8 cases with small R waves in leads V_1 and V and little or no R wave progression up to leads V or V_4 the R S ratio of the sagittal lead Z was found to be abnormal (less than 0 10) Such an abnormal ratio was also found in the case with a QS pattern in leads V_1 and V In 2 additional cases with QS waves in leads III and aV_F the determination of the R/S ratio of lead Y resulted in an abnormally low value (less than 0 93) Thus the application of normal standards for orthogonal leads showed that 8 cases out of 19 with discrepancies in findings were outside normal limits Even when these cases were discounted 11 records (4 2 per cent) remained where clinical information contained in the standard ECG could not be recovered from the 3 orthogonal leads

2 Comparison of the 12 standard leads with resolved orthogonal leads The next step in the correlation consisted in a comparison of the 12 standard leads with resolved leads derived from directions approximately comparable to those of the conventional ECG In 18 out of 19 cases in which clinically significant detail could not be recovered from the 3 basic orthogonal leads the resolved leads revealed this information Thus a complete correlation was found in 99 6 per cent of the total group

In the 8 cases with small R waves and little or no R wave progression in the right precordial leads the resolved leads showed an analogous sequence of small R waves in the XZ leads (Fig 3) In all cases with an RSR pattern in lead V_1 without counterpart in the sagittal lead Z the resolved leads to the right of this lead showed an RSR pattern (Fig 4) The 2 cases with significant Q waves in lead aV showed the same pattern in the corresponding resolved lead XY 150 Similar relationships were found in the 2 cases with QS waves in leads III and aV_F In the case shown in Fig 5 the R/S ratio of the vertical lead Y

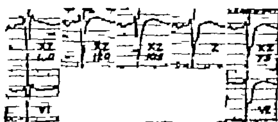


Fig 4 Standard lead V is of the RSR type The pattern together with a QRS duration of 0 14 sec led to the diagnosis of a right ventricular conduction defect The characteristic RSR pattern is not shown in lead Z It appears however in the resolved lead XZ 150 Note the angular discrepancy in effective electrical direction of lead V and V_2 This has been a frequent finding especially in right precordial leads

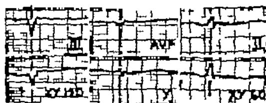


Fig 5 Standard lead III and aVF show no initial positivity and are essentially of the QS type (small terminal R wave can be seen in aVF) This record was interpreted as compatible with an old diaphragmatic infarct Orthogonal lead Y shows no Q wave but its R/S ratio is abnormal (less than 0.93) The resolved lead XY 120 resembles closely lead III and a similar relationship exists between leads II and XY 60 Note the angular discrepancy between lead aVF and Y The transition from a mainly positive to negative deflection lies approximately in the axis of Y The transition for the standard lead however is in between leads II and aVF i.e. further to the left

as mentioned before was abnormally low The resolved lead XY 120 corresponding to lead III showed the same QS pattern Both leads II and XY 60 had an RS configuration It is noteworthy to point out in this case the discrepancy between lead aVF (QS) and lead Y (rS) The amplitudes in both leads were very low and both were very close to the transition zone The standard leads revert from mainly positive deflections to mainly negative ones between leads II and aV_F A similar transition is seen in the resolved leads approximately at lead Y or very close to it Such discrepancies in direction between standard leads and corrected orthogonal leads were found frequently and have been discussed previously They are due to discrepancies between effective electrical lead directions of standard leads and those of corrected leads

A similar situation was encountered in the case with QS waves in leads V_1 and V The same pattern appeared in the resolved leads XZ 120 and 150 but not in the sagittal lead Z which showed only an abnormal R/S *ratio* The case with QS waves from lead V to lead V showed abnormally small R waves in leads XZ 105 to 45 and no initial R wave in lead *XZ 30* Lead *Z* showed an abnormal R/S ratio in this case (Fig 6)

The only case out of the total of 261 in which there was an apparent discrepancy in the content of clinical information between standard and resolved leads was the one mentioned previously as having an isolated T wave negativity in the precordial leads V_3 and V (Fig 7) T waves of lead *Z* were biphasic and negative in lead X Since this is an abnormal finding the T wave abnormality by itself would not have been missed in the orthogonal ECG The reproduction of this T wave change however cannot be considered close enough for a good correlation

All S T segment shifts found in the standard leads were also recovered in the resolved leads (Fig 8)

Discussion

Although good correlation between findings in the standard 12 lead ECG and resolved leads derived from a corrected orthog

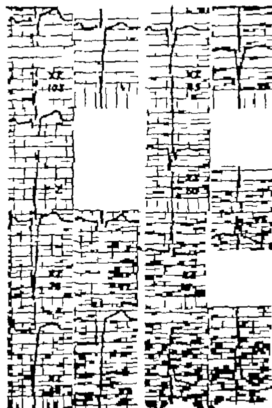


Fig 6 Standard leads V and V show very small initial R waves decreasing in amplitude toward the left Lead V and V are of the QS type The diagnosis of an old anterior wall infarct was made Orthogonal lead Z shows an rS pattern with an abnormal R/S ratio of less than 0.10 The resolved lead also lack an R wave progression toward the left and in lead XZ 30 the initial R is lost completely Note the sudden transition from QS in V to R in V The direction of XZ 30 appears to be in between the two

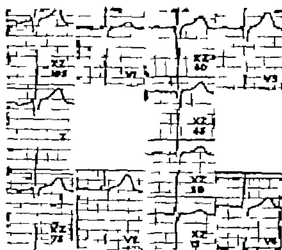


Fig. 3. Standard leads V[illegible] to V[illegible] are of the rS type and do not show any R wave progression. A sudden transition from rS to RS is seen in V[illegible]. The lack of R wave progression is also seen in the XZ leads from 105 to 30 with an analogous transition from rS to RS in XZ 15. The orthogonal lead Z of this record was found to be abnormal with an R/S ratio of less than 0.10. The broken vertical lines in this and the following figures indicate the R wave peaks in leads X and I which were taken as time reference leads for the two sets of tracings, respectively.

rS type. Another patient's record had QS waves in leads V_1 to V[illegible]. Neither the horizontal lead X nor the sagittal lead *Z* were found to be abnormal in configuration. A last case showed a so-called "isolated T wave negativity" in leads V_1 and V[illegible], i.e., T waves to the right and left of these leads were found to be upright. The orthogonal ECG showed mainly negative T waves both in leads X and Z. The T wave abnormality, therefore, was not recognized in the orthogonal leads.

After the correlation of patterns, the cases with deficiencies in clinical information in orthogonal leads were singled out for further analysis. The preliminary normal standards developed in this laboratory for Schmitt's SVEC III lead system were applied to these cases and deviations from normal ranges were noted. In 5 out of 8 cases with small R waves in leads V_1 and V[illegible] and little or no R wave progression up to leads V_3 or V_4 the R/S ratio of the sagittal lead Z was found to be abnormal (less than 0.10). Such an abnormal ratio was also found in the case with a QS pattern in leads V_1 and V[illegible]. In 2 additional cases with QS waves in leads III and aV_F the determination of the R/S ratio of lead Y resulted in an abnormally low value (less than 0.93). Thus, the application of normal standards for orthogonal leads showed that 8 cases out of 19 with discrepancies in findings were outside normal limits. Even when these cases were discounted, 11 records (4.2 per cent) remained where clinical information contained in the standard ECG could not be recovered from the 3 orthogonal leads.

2. *Comparison of the 12 standard leads with resolved orthogonal leads.* The next step in the correlation consisted in a comparison of the 12 standard leads with resolved leads derived from directions approximately comparable to those of the conventional ECG. In 18 out of 19 cases in which clinically significant detail could not be recovered from the 3 basic orthogonal leads the resolved leads revealed this information. Thus, a complete correlation was found in 99.6 per cent of the total group.

In the 8 cases with small R waves and little or no R wave progression in the right precordial leads the resolved leads showed an analogous sequence of small R waves in the XZ leads (Fig. 3). In all cases with an RSR' pattern in lead V_1 without counterpart in the sagittal lead Z, the resolved leads to the right of this lead showed an RSR' pattern (Fig. 4). The 2 cases with significant Q waves in lead aV_L showed the same pattern in the corresponding resolved lead XY 150. Similar relationships were found in the 2 cases with QS waves in leads III and aV_F. In the case shown in Fig. 5 the R/S ratio of the vertical lead Y

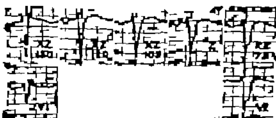


Fig. 4. Standard lead V[illegible] is of the RSR' type. This pattern, together with a QRS duration of 0.14 sec., led to the diagnosis of a right ventricular conduction defect. The characteristic RSR' pattern is not shown in lead Z. It appears, however, in the resolved lead XZ 150. Note the angular discrepancy in effective electrical directions of leads V[illegible] and V[illegible]. This has been a frequent finding especially in right precordial leads.

could have been produced by resolution of the leads This procedure consists only of linear combinations of the 3 basic orthogonal components i e a special type of transformation of data without derivation of new data from the patient In this fashion the familiar ECG patterns of the 12 lead ECG can be reproduced providing identical clinical information The practically complete correlation between standard and resolved leads indicates therefore that discrepancies found in the first comparison with 3 leads only were due to differences in the display of data rather than to deficiencies in the recording of electrical information It is safe to assume that the display of data in the form of vector loops which was not included in the present study would have revealed all of the abnormalities recovered from resolved leads This is obvious because resolved leads can easily be derived from the conventional 3 plane projections used in vectorcardiography (frontal sagittal and horizontal planes)

The good agreement between clinical information derived from the standard 12 lead ECG and the resolved orthogonal 3 lead ECG cannot necessarily be taken as supportive evidence for any hypothesis of a current generator equivalent such as the dipole theory The conventional diagnostic criteria are too crude to be used for such arguments If the orthogonal leads had suppressed electrical information from the body surface to any appreciable extent one should have expected however considerable discrepancies in findings A relatively simple generator equivalent such as a dipole shifting in location during the cardiac cycle[14, 4] could explain the good correlation between standard and orthogonal leads

From the present large series of patients with ECG abnormalities it can be concluded that the clinical information of the standard 12 lead ECG can only be recovered from a corrected orthogonal 3 lead ECG by resolution of the 3 basic orthogonal components and/or vector loop representation This indicates that the clinical information is contained in the 3 lead ECG but cannot be recognized without transformation of data Replacement of the standard 12 lead ECG by a resolved orthogonal 3 lead ECG may not appear to be practical in routine clinical electrocardiography It has become of major importance however in attempts to analyze electrocardiograms automatically by means of electronic computers [8] Reduction of data and elimination of redundant information has to precede computation proper for technical reasons [16] Such a sequence is mandatory because of limitations in analog to digital conversion facilities and computer memory capacity Although reduction of data of multichannel analog information such as the 12 lead electrocardiogram can be performed by electronic computers[17] prior to analysis of data such a sequence is impractical and uneconomical on a large scale basis Once the reduced information is stored in the computer memory however transformation of data such as resolution of orthogonal leads can be performed merely by writing a proper set of instructions for the computer

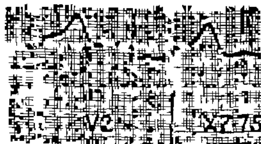


Fig 8 S-T shift in standard lead V and resolved lead XZ 75 Although minor discrepancies in S-T shifts between standard and orthogonal leads were seen occasionally all S-T abnormalities were clearly recognized both sets of tracings



Fig 9 Similar to Fig 7 this record illustrates discrepancies in the level of standard precordial and resolved XZ lead Lead YZ 330 resembles very closely lead V although the former is locate 30 degrees bove the XZ level

Since it has been shown that corrected leads exceed conventional bipolar and unipolar leads in constancy of effective lead direction and strength, their greater consistency in performance may enhance the reliability of electrical data recorded from patients. Evidence of superiority in *diagnostic accuracy* of the corrected orthogonal ECG cannot be derived from the present study, however, because the content of clinical information of the conventional 12 lead ECG was used as the only criterion for comparison.

Summary

The clinical information contained in the standard 12 lead ECG was compared with that in the corrected orthogonal 3 lead ECG in 261 randomly selected patients who showed ECG abnormalities. In a *first correlation*, all electrical information of clinical significance in the 12 standard leads could not be recovered from the 3 orthogonal leads in 7.3 per cent of all cases. In a *second* correlation, orthogonal leads were resolved in order to obtain additional leads from directions comparable to those of standard records. This procedure led to good agreement in all cases except one with a questionable discrepancy. Since lead resolution merely represents a different type of display of the data of orthogonal leads, resolved records do not contain any new information not contained in the 3 basic leads. The conclusion, therefore, was that the informational content of 3 corrected orthogonal leads is comparable to that of the standard 12 lead ECG. Transformation of data, such as orthogonal lead resolution and/or vector loop display, appears to be necessary, however, to recover without appreciable loss the clinical information contained in the standard 12 lead electrocardiogram.

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REFERENCES

1. Pipberger, H. V.: Current status and persistent problems of electrode placement and lead systems for vectorcardiography and electrocardiography, Prog. Cardiovas. Dis. 2:248, 1959.
2. Pipberger, H. V., Freis, E. D., Taback, L., and Mason, H. L.: Preparation of electrocardiographic data for analysis by digital electronic computer, Circulation 21:413, 1960.
3. Taback, L., Marden, E., Mason, H. L., and Pipberger, H. V.: Digital recording of electrocardiographic data for analysis by a digital computer, I.R.E. Tr. Medical Electronics ME-6:167, 1959.
4. McFee, R., and Johnston, F. D.: Electrocardiographic leads. I. Introduction, Circulation 8:554, 1953.
5. Helm, R. A.: Theory of vectorcardiography: A review of fundamental concepts, Am. Heart J. 49:135, 1955.
6. Hartmann, I., Veyrat, R., Wyss, O. A. M., and Duchosal, P. W.: Comparaison vectorielle des électrocardiogrammes unipolaires recueillis en deux points du plan transversal équidistant du centre et opposés par rapport au coeur, Cardiologia 24:317, 1954.
7. Grant, R. P., and Estes, E. H.: Spatial vector electrocardiography, Philadelphia, 1952, Blakiston Company.
8. Schmitt, O. H., Levine, R. S., Simonson, E., and Dahl, J.: Electrocardiographic mirror pattern studies, Am. Heart J. 45:416, 500, and 655, 1953.
9. Frank, E.: Measurement and significance of cancellation potentials on the human subject, Circulation 11:937, 1955.
10. Frank, E.: Critical experiment in electrocardiography, Science 122:783, 1955.
11. Brody, D. A., and Copeland, G. D.: Electrocardiographic cancellation. Some observations concerning the nondipolar fraction of precordial electrocardiograms, Am. Heart J. 56:381, 1958.
12. Okada, R. H.: Multiple dipole representation of the human heart for vectorcardiography, Science 127:240, 1958.
13. Morton, R. F., Romans, W. E., and Brody, D. A.: Cancellation of esophageal electrocardiograms, Circulation 15:897, 1957.
14. Okada, R. H., Langner, P. H., Jr., and Briller, S. A.: Synthesis of precordial potentials from the SVEC III vectorcardiographic system, Circulation Res. 7:185, 1959.
15. Nelson, C. V., and Hecht, H. H.: Investigation of horizontal component of heart vector by means of circumferential chest leads at mid-ventricular level, Fed. Proc. 14:107, 1955.
16. McFee, R., and Parungao, A.: On the interpretation of cancellation experiments. I and II, Am. Heart J. 58:582, 1959; 59:433, 1960.
17. Scher, A. M., Young, A. C., and Meredith, W. M.: Factor analysis of the electrocardiogram. A test of electrocardiographic theory: Normal hearts, Circulation Res. 8:519, 1960.
18. Duchosal, P. W., and Grosgurin, J. R.: The spatial vectorcardiogram obtained by use of a trihedron and its scalar comparisons, Circulation 5:237, 1952.
19. Milnor, W. R., Talbot, S. A., and Newman, E. V.: A study of the relationship between unipolar leads and spatial vectorcardiograms using the panoramic vectorcardiograph, Circulation 7:545, 1953.
20. Frank, E.: An accurate, clinically practical system for spatial vectorcardiography, Circulation 13:737, 1956.

21 Abildskov J A Street W W Solomon E and Toomajian A H Clinical observations with the Frank precordial lead system Circulation I 1069 1958
22 Schmitt O H and Simonson E The present status of vectorcardiography Arch Int Med 96 5 4 1955
23 Pipberger H V and Wood C R J A simplified method for the resolution of the orthogonal electrocardiogram Circulation Res 6 239 1958
24 Pipberger H V and Lilienfield L S The application of corrected electrocardiographic lead systems in man Am J Med 25 539 1958
25 Pipberger H V The normal orthogonal electrocardiogram and vectorcardiogram with a critique of some commonly used analytic criteria Circulation I 1102 1958
26 Pipberger H V and Tanenbaum H L The P wave P R interval and Q T ratio of the normal orthogonal electrocardiogram Circulation 18 11 5 1958
27 Burger H C and van Milaan J B Heart vector and leads I II and III Brit Heart J 8 15 1946 9 154 1947 10 229 1948
28 Frank E Spread of current in volume conductors of finite extent Ann New York Acad Sc 65 980 1957
29 Langner P H Jr Dewees E J and Moore S R A critical and comparative analysis of methods in electrocardiography employing area QRS and T vectors Am Heart J 46 183 1953
30 Pipberger H V and Freis E D Automatische Analyse kardiologischer Analog Daten mittels elektronischer Rechenmaschinen Med Dok 4 58 1960

Relation of myocardial bridges and loops on the coronary arteries to coronary occlusions

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In 1951 a study by Geiringer entitled "The Mural Coronary" appeared in the *American Heart Journal*.[1] Independently, I began to occupy myself with the same subject. Although there is an extensive literature concerning the course of the coronary arteries, little is known about the relation of their course to the heart muscle. The big stem of the coronary arteries very often disappear under the superficial myocardial fibers for a shorter or longer course and then emerge on the surface of the heart again.

Brief mention of this phenomenon has been made by Reyman, Tandler,[4] Crainicianu, and Djavakhishvili and Komakhidze. The only authors who occupy themselves with the subject are the above-mentioned Geiringer, who distinguishes the mural and the epicardial courses of the artery, and Edwards, Burnsides, Swarm, and Lansing.[11] Recently Porstmann and Iwig diagnosed this intramural stretch of the coronary artery in a patient by means of serial coronarograms.

Because these muscular fibers which lie upon the artery might have an influence on the passage of the blood through the artery, our first study was based upon the macroscopic appearance and occurrence of these muscular overbridgings. Further study concerned their relationship to some physical marks[8] and finally their microscopic relationship to the wall and structure of the artery.[1-11] The present work is a summary of our up-to-date experience.

Materials and methods

The observations are based upon a detailed preparation of the coronary arteries of 70 hearts of persons who ranged in age from newborn to 80 years. In more than half of the cases the coronary arteries were filled with colored gelatin in order to make their course more distinct.

A microscopic study of sections from 36 hearts was undertaken; staining was done with hematoxylin-eosin, after van Gieson, and with green trichromic, which proved to be the best for our purpose.

In order to determine the thickness of the intima, the magnified sections were drawn on paper of constant thickness (0.28 μ) and by weighing the whole wall of the artery and then the intima we ascertained what proportion the intima comprised of the whole wall of the artery. The other way to determine the thickness of the intima was the direct micromeasurement of minimum and maximum thickness of it in all sections. Both of these methods gave the same results as to the proportion of the thickness of the intima and the wall of the artery, i.e., they gave the picture of the degree of hyperplasia of the intima. The latter method allowed the study of the degree of inequality of this hyperplasia.

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Macroscopic findings

The muscular formations which overbridge the arterial course exist in two forms viz muscular bridges and muscular loops

Bridges occur in the course of the coronary arteries over the ventricular myocardium They can be seen after the removal of subepicardial fat tissue (Fig 1) The artery often dips under the superficial layer of ventricular myocardium and after a shorter or longer course under the muscle it appears on the surface again The length of such a muscular bridge may be 3 to 69 mm most often however it is 20 to 30 mm In some cases the muscular fibers may be very close on the adventitia of the artery whereas in other cases there is interstitial fat tissue between the bridge and the adventitia (Fig 3) The thickness varies up to 5 mm

The muscular loops occur in the course of arteries in the atrioventricular groove (Fig 2) They are formed by muscular fibers of the atrial myocardium which vault from the wall of the atrium embrace the artery up to three fourths of its wall circumference and then return into the atrial myocardium (Fig 4) In all cases they have a close relation to the adventitia of the artery and their length is 2 to 30 mm most often 10 to 15 mm They are thinner than the muscular bridges and therefore their preparation is more difficult Their thickness is 100 to 300 μ

In 70 hearts we found a total of 167 muscular overbridgings among them 108 bridges and 59 loops The greatest number of these formations in one heart was 6 In only 10 hearts were none of the muscular formations observed These formations are bound to certain places where they have a certain frequency of occurrence (Fig 5) The most frequent place of occurrence is *the proximal half of the an*terior descending branch of the left coronary artery during its course in the interventricular groove the muscular bridge in this location appears in 60 per cent of all cases In this locality bridging may also be doubled but rarely tripled The other branches are overbridged less often the oblique branch of the left coronary artery *in* 18 5 per cent the *marginal branch in* 14 2 per cent and the terminal branches of the left coronary artery on the diaphragmatic heart surface in no more than 7 1 per cent of the cases

The most frequent place of occurrence of the muscular loop is in the course of the circumflex branch of the left coronary artery in the atrioventricular groove where the artery curves the obtuse margin Here the occurrence is 40 per cent

The *left* coronary artery and its branches possess the muscular formations in 7 1 per cent of the cases whereas the right coronary artery is overbridged less frequently i e in only 41 4 per cent The difference becomes still more striking by a comparison of the whole number of the muscular formations found Of 167 of them there were 121 in the region of the left coronary artery (72 5 per cent) and 46 in the region of the right coronary artery (27 5 per cent)

The right coronary artery in the atrioventricular groove is embraced by muscular fibers too however they are weaker and shorter They occur less frequently on the curve of the artery over the acute *margin (in only 8 5 per cent of the cases)* occurrence is more frequent in the terminal part where the artery is crossed by the medial heart vein after it has given off its posterior descending branch There the loops are present in 27 1 per cent of the cases as the most frequent muscular formation in the region of the right coronary artery and as the third most frequent location in the heart as a whole Thus loops overbridge the terminal branches of the right coronary artery which supplies the posterior part of the left ventricle

The muscular bridges of the branches of the right coronary artery are rarer and more variable in their form and location they are found in 2 8 to 11 4 per cent of the cases

Microscopic findings

A close relationship of muscular fibers to the adventitia of the artery can be observed very often in bridges but always in loops In some cases even transition of the joints of muscular fibers into fibrous tissue of the adventitia can be observed or the muscular fibers run directly *the* adventitia in a certain stret artery





Fig 1 Muscular bridge ( ) on the anterior descending branch of the left coronary artery (b)

Fig 2 Muscular loop ( ) on the right coronary artery (b)

Muscular fibers of the described formations run mostly in the same direction and usually cross the artery obliquely In loops it was possible to observe in some cases two layers of muscular fibers (circular and longitudinal) in one case there were even three layers

In older persons the muscular loops could change the muscular tissue was transformed into collagen tissue In such a fibrous loop the muscular tissue is preserved only in some places

Furthermore we concerned ourselves with the influence of the muscular formations (especially the most frequent formation i e the bridge on the anterior descending branch of the left coronary artery) on the media and the intima of the artery

The thickness of the media in 14 cases observed comprised 20 to 40 per cent of the whole wall of the artery before the bridge 25 to 50 per cent under the bridge and 30 to 45 per cent behind the bridge Thus it comprises approximately one third of the thickness of the wall of the vessel in all three stretches observed and does not vary essentially

Interesting differences can be observed in the intima (Table I) Before the bridge it occupied 33 8 per cent of the surface of the section under the bridge only 20 6 per cent and behind the bridge 22 9 per cent in our 14 cases The difference of the surface before and under the bridge appears to be statistically significant Also the relationship between the minimum and maximum thickness of the intima is similar Before the bridge the intima makes up 22 8 to 54 6 per cent of the wall of the artery whereas under the bridge it makes up only 13 0 to 35 8 per cent and behind the bridge 17 1 to 36 7 per cent In the stretch of the artery before the bridge the intima is thus much thicker than under the bridge whereas behind the bridge it is of the same thickness or a little thicker

Most important however is the comparison of the same stretches of a bridged and unbridged artery before the bridge (Table II) We examined 8 unbridged and 16 bridged arteries The surface measurements gave the same results in both instances in the unbridged artery the surface of the intima was on the average 35 9 per cent of the whole wall of the artery

and in the bridged artery it was 35.6 per cent. But a quite different result was obtained by a comparison of the minimum and maximum values of the thickness of the intima in per cent of the whole wall. In the unbridged artery the average minimum was 33.5 per cent and the average maximum was 1 9 per cent; in the bridged artery the average minimum was 26.0 per cent and the average maximum was 56.8 per cent. In the bridged artery the minimum value was lower whereas the maximum value on the other hand was higher. If the difference between the minimum and maximum is only 14.4 per cent in an unbridged artery, in a bridged artery it is as much as 30.8 per cent. The statistical evaluation of these differences shows a high significance. From this it follows that hyperplasia of the intima in a bridged artery before the bridge shows a much greater irregularity than in an unbridged artery at the same level. The same result gives measurement of the thickness of the intima of the bridged anterior descending branch of the left coronary artery and of its unbridged oblique branch before the bridge (Table II): both arteries were visible in one and the same section. In all of the cases observed the difference between the minimum and the maximum thickness of the intima was greater in the bridged descending branch (34.4 per cent) than in the unbridged oblique branch (17.8 per cent). In this case too the difference is close to the limit of statistical

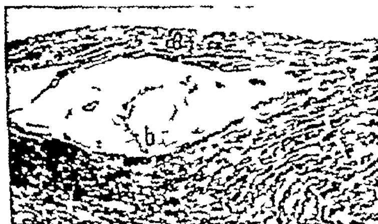


Fig. 3 Section of muscular bridge (a) on the anterior descending branch of the left coronary artery (b)



Fig. 4 Section of muscular loop ( ) on the circumflex branch of the left coronary artery (b)



Fig 1 Muscular bridge (a) on the anterior descending branch of the left coronary artery (b)

Fig 2 Muscular loop (a) on the right coronary artery (b)

Muscular fibers of the described formations run mostly in the same direction and usually cross the artery obliquely In loops it was possible to observe in some cases two layers of muscular fibers (circular and longitudinal) in one case there were even three layers

In older persons the muscular loops could change the muscular tissue was transformed into collagen tissue In such a fibrous loop the muscular tissue is preserved only in some places

Furthermore we concerned ourselves with the influence of the muscular formations (especially the most frequent formation i e the bridge on the anterior descending branch of the left coronary artery) on the media and the intima of the artery

The thickness of the media in 14 cases observed comprised 20 to 40 per cent of the whole wall of the artery before the bridge 25 to 50 per cent under the bridge and 30 to 45 per cent behind the bridge Thus it comprises approximately one third of the thickness of the wall of the vessel in all three stretches observed and does not vary essentially

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Fig 3 Section of muscular bridge (a) on the anterior descending branch of the left coronary artery (b)

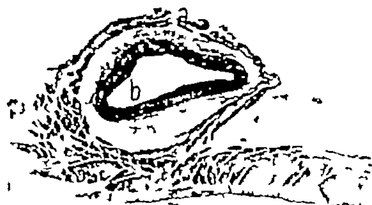


Fig 4 Section of muscular loop ( ) on the circumflex branch of the left coronary artery (b)

Table I Anterior descending branch of the left coronary artery The thickness of the intima in per cent of the whole wall

	Number of cases	Minimum maximum thickness (arithmetic average)	Difference between minimum and maximum	Surface (arithmetic average)	Statistical significance of differences the surfaces (t test after Fisher)
Before the bridge	14	22 8–54 6	31 8	33 8	t = 3 06 p < 0 01 Statistically significant
Under the bridge	14	13 0–35 8	2 8	20 6	
Behind the bridge	14	17 1–36 7	19 6	22 9	

Table II Bridged and unbridged coronary artery The hyperplasia of the intima in per cent of the whole wall in the stretch before the bridge

	Number of cases	Surface (arithmetic average)	Minimum maximum thickness (arithmetic average)	Difference between minimum and maximum	Statistical significance of differences between minimum and maximum (t test after Fisher)
Unbridged anterior descending branch	8	35 9	33 5–47 9	14 4	t = 98 p < 0 01
Bridged anterior descending branch	16	55 6	26 0–56 8	30 8	
Bridged anterior descending branch	7	——	23 2 57 6	34 4	t = 2 59 p < 0 05
Unbridged oblique branch	7	——	29 3–47 1	17 8	

significance although the number of cases is very small

Schematically demonstrated (Fig 6) the bridge effects the unequal hyperplasia of the intima in the proximal stretch of the artery whereas on the distal stretch it has no influence here the artery behaves in the same manner as do other arteries lying subepicardially

Especially interesting was one case in which the anterior descending branch divided into three branches (trifurcation) and each of these branches had a different course (Fig 7) The sclerotic obliterated artery (*1*) entered under a very long bridge the artery with unchanged intima (*2*) had only a subepicardial course and the artery with moderately thickened intima (*3*) dipped under a smaller bridge. Here the fate of the intima corresponded exactly with the presence of the bridge.

Discussion

In the literature the frequency of the overbridgings is mentioned by Geiringer[1] in the anterior descending branch of the left coronary artery where the author found the bridge in 23 out of 100 cases In our material a bridge occurred in 60 per cent of the cases at the place mentioned this is a much higher incidence Edwards Burnsides Swarm and Lansing[12] found the overbridgings in 5 4 per cent of all hearts (15 times in 276 hearts) Djavakhishvili and Komakhidze[3] observed these formations in half of all hearts observed whereas in our material they were found in 85 per cent of the cases We could confirm the observation of these latter authors that these formations are more frequent in the region of the left coronary artery than in the region of the right one The muscular loops have

not yet been described in the literature

It is known in regard to the coronary arteries that the most frequent occlusions occur in the first place in the proximal part of the anterior descending branch of the left coronary artery in the second place in the proximal stretch of the circumflex branch of the left coronary artery before the obtuse margin and in the third place in the terminal stretch of the right coronary artery at the origin of its posterior descending branch (Koch and Kong[1]) These places correspond to the stretches of the arteries before the sites *of the most frequent occurrence of muscular overbridgings* even in the same succession

No difference was found in the occurrence of the bridges and loops in different age groups This fact means that these formations are already present in newborn infants and on the basis of our own sections they are present even in the fetus They develop as early as the embryonic period at the time of the formation of the coronary arteries from the original capillary network This opinion we share with Geiringer In agreement with him we find no differences between the sexes Nevertheless there is some tendency to a greater number of overbridgings in the region of the left coronary artery in men than in women (82 5 to 70 0 per cent) [*]

Furthermore we find some relation of the muscular formations to the length of body and to the physical type In tall and thin persons the muscular bridges and loops are more frequent in the region of the left coronary artery than they are in short and thick persons On the contrary in the region of the right coronary artery the overbridgings appear more often in short and thick persons than in tall and thin persons [*]

From the autopsy records of the Institutes of Forensic Medicine and of Pathologic Anatomy of our Medical Faculty

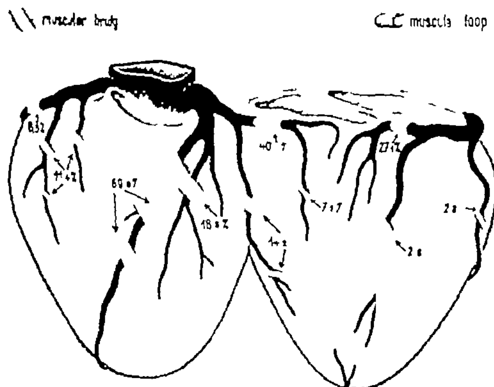


Fig 5 Occurrence of muscular bridges and loops on the coronary arteries in per cent (by V Gabrielová)

we ascertained that anterior myocardial infarction really occurs more often in tall and thin persons whereas posterior myocardial infarction is relatively more frequent in short and thick persons

The clue to these coincidences between the described muscular formations and occlusions of coronary arteries is given in the results of microscopic study In agreement with Geiringer we state that the bridge does not affect the media of the artery but it affects its intima Diffuse hyperplasia of the intima as a manifestation of the aging of the vessel becomes more and more intensive during the growth The bridge affects the intima favorably in that direction in that it hinders this hyperplasia We observed this phenomenon by two methods other than Geiringer's and can therefore confirm his observation that the intima in the subepicardial stretches of the artery is hyperplastic whereas in the mural stretches (i.e. under the bridge) it remains thin On the other hand we could not agree with the findings of Edwards Burnsides Swarm and Lansing[11] who did not observe any difference between the sclerotic process in the intramural (i.e. under the bridge) and that in the extramural (i.e. subepicardial) portions of the coronary arteries

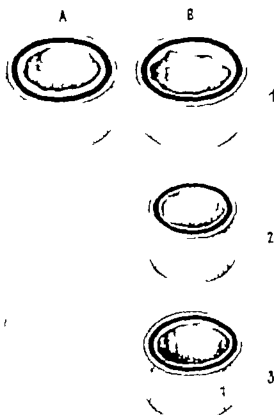
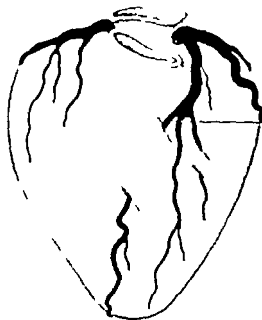


Fig 6 Thickness of the intima in an unbridged (A) and bridged (B) anterior descending branch of the left coronary artery before (1) under (2) and behind (3) the bridge (Drawn by V Gabrielova)

But first of all we aimed at the difference between the bridged and unbridged artery in that stretch in which occlusions most often occur Even if the degree of intimal hyperplasia is the same in both cases there is a marked difference in the form of this hyperplasia In an unbridged artery the hyperplasia is more regular whereas in a bridged artery it is strongly irregular—the thin places of the intima alternate with hyperplastic intima and sclerotic plaques are formed Irregular hyperplasia could be observed even in a 15 year old person in our material This finding can be explained by the effort exerted by the wall before the bridge in connection with the constriction of the artery in systole which is evident from the observation of Porstmann and Iwig These authors found in the proximal stretch of the course of the anterior descending branch rhythmical constrictions of the artery in every systole during the serial coronarogram in a 19 year old patient In this way a site of predilection is developed (one of the morphologic conditions for the manifestation of the sclerotic process) for the forming of sclerotic plaques and occlusions

We are far from considering the bridges and loops as a cause of occlusions of the coronary arteries These formations exist in most persons (in 85 7 per cent) and they exist on the basis of our own observations in various animals even if the sclerotic process of the coronaries which is typical of man does not occur in these animals to such a degree In the heart of the horse and the cow the coronary arteries lie subepicardially but only the terminal branches *of second and third order* are occasionally bridged On the contrary in the rabbit guinea pig and rat the arteries run intramurally from the beginning The same conditions found in man are found



Fig



Fig 7 Section through the anterior descending branch of the left coronary artery and its branches See text for explanation (Diagram on left by V Gabrielov)

in the dog and especially in macaques In sheep and goats the subepicardial and myocardial stretches of the artery alternate even more often than in man and the number of bridges and their size are much greater[1] In spite of this fact these animals do not suffer from such a sclerotic process of the coronaries and from myocardial infarctions as are known in man

Schematically formulated the proper cause of the sclerotic process lies in the changes of metabolic processes under the influence of some not yet quite well known noxious effects which manifest themselves as hyperplasia of the fibrous tissue or as lipoid infiltration of the intima The bridges and loops however form a suitable morphologic condition for the development of this process Only in this way can we explain the striking relationship between the localization of the most frequent occlusions of the coronary arteries and the stretches of the artery behind which the described formations occur most often

Summary

1 The muscular overbridgings on the coronary arteries of 70 human hearts are described and classified into (a) muscular bridges under which the artery submerges during its course over the surface of the ventricles and (b) muscular loops which attach the artery to the atrial myocardium during its course in the atrioventricular groove These formations occur in 85 ? per cent of all hearts the occurrence is more frequent in the region of the left coronary artery

2 The muscular bridges formed by ventricular myocardium—usually 10 to 20 mm long up to 5 mm thick and rarely mentioned in the literature—are most frequent in the proximal half of the anterior descending branch (60 0 per cent) next most frequent in the oblique branch of the left coronary artery (18 5 per cent) and rarer (2 8 to 14 2 per cent) in other branches of the left and right coronary arteries

3 The muscular loops formed by atrial myocardium—usually 10 to 15 mm long 100 to 300 µ thick and not mentioned in the literature up to now—are most frequent in the first stretch of the circumflex branch of the left coronary artery (40 0 per cent) and in the terminal stretch of the right coronary artery (27 1 per cent)

4 The stretch of the artery before the bridge or loop corresponds to the sites at which occlusions most frequently occur just as the order of frequency is the same as that of the occurrence of these formations (the origin of the anterior descending branch the proximal stretch of the circumflex branch of the left and the terminal stretch of the right coronary arteries)

5 Microscopic examination of 36 hearts showed a very close relationship of the muscular formation to the advent

The muscular overbridging may have more layers (circular and longitudinal). In the muscular loops fibrous degeneration in old persons was observed to greater or smaller degree.

6. The intima of the artery under the bridge is normally thin, whereas especially before the bridge it is strongly hyperplastic, but sometimes also behind the bridge.

7. The degree of hyperplasia of the intima in unbridged and bridged arteries before the bridge (most frequently the site of occlusions) is compared. As to the surface of the sections hyperplasia of the intima is of the same degree, but there is a difference in its shape. Hyperplasia of the intima in the unbridged artery is more regular, whereas in the bridged artery it is irregular and there is a greater tendency to the formation of sclerotic plaques.

8. The stretches of the arteries before the muscular bridges and loops could become one of the morphologic conditions, a site of predilection for a sclerotic process. In this way the coincidence between sites of the most frequent overbridgings and those of the most frequent occlusions of the coronary arteries could be explained.

REFERENCES

1. Geiringer, E.: The mural coronary, Am. Heart J. 41:359, 1951.
2. Reyman, H. Ch.: Dissertatio de vasis cordis propriis, Haller Biblioth. anat. 2:366, 1737.
3. Tandler, J.: Anatomie des Herzens, Jena, 1913, Fischer, p. 220.
4. Crainicianu, A.: Anatomische Studien über die Coronararterien und experimentelle Untersuchungen über ihre Durchgängigkeit, Virchows Arch. f. path. Anat. u. Physiol. 238:1, 1922.
5. Djavakhishvili, N. A., and Komakhidze, M. E.: Applied morphology of heart vessels (Russian Text), Tezisy dokladov VI vsesoyuznogo syezda anatomov, gistologov i embriologov, Kiyev, 565, 1958.
6. Porstmann, W., and Iwig, J.: Die intramurale Koronarie im Angiogramm, Fortschr. Röntgenstr. 92:129, 1960.
7. Poláček, P.: Muscular bridges and loops on coronary arteries of man (Czech text), *Sdělení na II. konferenci Č. morfologů—Smolenice 1958*, Č. morfologie 7:119, 1959.
8. Poláček, P.: Über die myokardialen Bündel, die den Verlauf der Koronararterien überbrücken, Anat. Anzeiger 106:386, 1959.
9. Poláček, P.: Relation of muscular bridges and loops on coronary arteries to some physical marks in man (Czech text), Sborník lékař. lék. fakulty KU v Hradci Králové 3:[illegible] 1960.
10. Poláček, P.: Myocardial bridges and loops on the coronary arteries in man. Abstract from inaugural dissertation (Czech text), Sborník lékařské fakulty KU v Hradci Králové—Supplementum 2-3, 1960 (in press).
11. Poláček, P.: Microscopical observation of the muscular bridges and loops on the human coronary arteries (Czech text), Čs. morfologie, 8:345, 1960.
12. Koch, W., and Kong, L. Ch.: Über die Formen des Coronarverschlusses, die Änderungen im Coronarkreislauf und die Beziehungen zur Angina pectoris, Beitr. z. path. Anat. u. allgem. Pathol. 90:21, 1932.
13. Edwards, J. C., Burnsides, Ch., Swarm, R. L., and Lansing, A. I.: Arteriosclerosis in the intramural and extramural portions of coronary arteries in the human heart, Circulation 13:235, 1956.

Hydrogen platinum electrode system in detection of intravascular shunts

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Recent advances in cardiovascular surgery have emphasized the need for more accurate techniques in preoperative diagnosis of cardiac abnormalities. The limitations of the oxygen method in this study of shunts are well known. More accurate techniques employing the indicator-dilution principle have been developed.[1-3]

Recently Clark described a method of labeling blood in the lung by means of hydrogen inhalation. As it reaches the right heart, the hydrogen-labeled blood is detected by a change in oxidation potential as registered by the platinum electrode at that site. The present report describes a modification and extension of the Clark technique with studies in 34 patients in whom intravascular shunts were confirmed or suspected. In addition, the comparative sensitivity of the hydrogen, dye-dilution, and oxygen methods was evaluated in 5 dogs with subclavian-pulmonary arterial anastomoses.

Methods and materials

Electrodes. Standard Goodale No. 5 and 6 intracardiac catheters were modified in order to introduce a shielded insulated conductor to an exposed platinum tip without occluding the side holes or affecting the autoclavability of the catheter. A bead made at the tip of a piece of platinum wire was spot soldered to a length of No. 32-41 polyurethane insulated magnet wire.† The bare metal was dipped in epoxy resin‡ and baked to complete the insulation. The wire was then drawn through the catheter from tip to butt and through the wall of the catheter near the butt end with a sewing needle. Epoxy resin was applied to seal the bead in the tip and the hole in the catheter wall. During baking, the conductor was displaced from the side holes by a Teflon plug. The wire which penetrated the wall of the catheter was soldered to the center conductor of a subminiature Teflon insulated coaxial cable§ which was 3 to 4 inches in length. This solder junction was insulated with epoxy. The shield from the cable was wrapped around the catheter. Nylon thread was wound around the junction, and a solution of polyvinyl chloride was applied fusing the junction to the wall of the catheter. A subminiature gold plated Tef

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†General Cable Corp., Bayonne, N.J.
‡Products Research Corp.
§Amphenol No. RG 188/u.

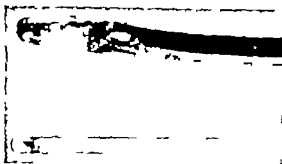


Fig 1 Catheter tip demonstrating position of platinum bead and epoxy resin with maintenance of lateral opening. Stylet tip for Cournand intra arterial needle indicating platinum tip with epoxy insulation band

lon insulated connector* was attached to the free end of the cable An autoclavable extension was made of the same cable and connectors The platinum tip was exposed and shaped with a jeweler s file The platinum electrode was blacked by cathodizing briefly in a chloroplatinic acid solution (Fig 1)

Probes for Cournand and Henry needles were similarly constructed A bead was formed on an appropriate length of platinum wire which had been pulled to 30 F gauge for the Cournand needle and 41 F gauge for the Henry needle This length was insulated by several thin applications of epoxy or polyurethane resin It was then inserted through epoxy filled stainless steel tubing The resin was polymerized fixing the platinum The tip of platinum wire was spot soldered to the coaxial cable epoxy insulated and covered with the shield which was embedded in an epoxy bead This bead rigidly fixed the cable to the stainless steel tubing The protruding platinum bead was shaped with a jeweler s file and burnishing tool to conform to the shape of the needle tubing The protrusion of the probe tip beyond the shell of the outer needle was adjusted by a Teflon spacer (Fig 2)

Electrical circuit Adequate measurement of oxidation potentials requires a higher impedance device (in order to avoid loading the half cell) than is found in most recording instruments which have an input impedance of about 1 megohm A simple one tube per channel battery operated DC coupled cathode follower circuit with an input impedance of 22 megohms was constructed (Fig 3) Although this circuit had a voltage amplification of less than unity (approximately 0 6) the resultant signals were larger because of reduced loading This also makes the signal less dependent on the size of the electrode (Fig 4) A standard calomel saturated KCl electrode was used as a common reference and was simply wrapped in gauze taped to the skin of the patient and wet with saline

Clinical studies Thirty four patients were studied with the hydrogen electrode the double catheter dye dilution and oxygen techniques The platinum tipped catheter was passed from an arm vein into the pulmonary artery The platinum tipped stylet was inserted through an intra arterial needle and proper electrical connections were made by means of sterile extension cords A platinum or rhodium plated nosepiece was taped in place on the nasal mucosa The patient took one breath of hydrogen and the changes in oxidation potential were monitored and recorded as continuous curves on an eight channel recorder The presence of a left to right shunt was readily detected from the early appearance of hydrogen in the right heart or pulmonary artery as compared with the time of appearance in the femoral artery Pressure was simultaneously recorded Approximately 2 to 4 minutes were required for the curves to return to the base line This procedure was repeated in each chamber of the right heart in order to localize the shunt

Two patients with pulmonary stenosis and atrial septal defect and 1 patient with ventricular septal defect had right to left shunts These patients were studied after rapid manual injection of 10 to 15 c c of blood or saline which had been exposed to hydrogen for 2 to 3 minutes The labeled blood or saline was injected into a cardiac catheter which had been placed upstream from the site of the right to left shunt and the hydrogen was detected by the electrode stylet in the systemic artery Similar studies were performed by means of injection of Cardiogreen dye with

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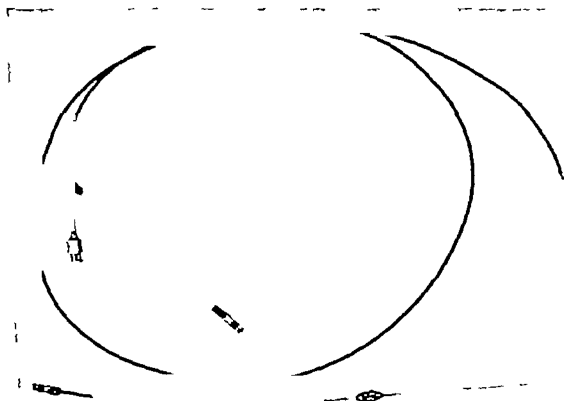


Fig Cardiac catheter and intra arterial stylet th platinum electrodes in tips

detection of the appearance of the charac teristic two peaks in the systemic arterial curve

Experimental studies The left subclavian artery was anastomosed to the pulmonary artery in 5 mongrel dogs A Jacobson inflatable cuff was placed about the sub clavian artery and the injection arm was implanted subcutaneously Approximately 2 weeks after recovery the animals were studied under intravenous Nembutal an esthesia and endotracheal intubation A No 5 or 6 Goodale catheter with a plati num tipped electrode was passed into the left pulmonary artery A second No 6 Goodale catheter without an el ctrode was passed nto the same position Another No 6 Goodale catheter w then passed into the right ventricle A Cournand needle was placed n the femoral artery The cuff which had previously been inflated with 2 to 3 c c of water to completely occlude the shunt was deflated in stages removing 0 05 c c at a t me until the hydrogen platinum system detected a shunt The platinum electrode ter was then carefully passed peripherally to avoid disturbing the other two catheters Dye curves were obtained from the pulmo nary artery and femoral artery after in jection of 1 25 mg of indocyanine dye into the platinum electrode catheter which had been placed in a peripheral pulmonary artery The calibration of the pulmonary curve was such that a deflection of 1 cm equaled 0 017 mg of Cardiogreen dye per liter of blood Blood was also withdrawn from the left pulmonary artery and right entricle for analysis of oxygen content A shunt was considered to be present when the difference in ox gen between the sample from the pulmonary artery and that from the right ventricle was 0 5 olume per cent The cuff was then deflated stepwise until both methods ind cated the presence of a shunt The relationship of the ap pearance of a shunt in these methods and the appearance of the murmur was noted The femoral arterial pressure was not altered during the procedure

In one dog a plat num electrode cathete was passed into the pulmonary art

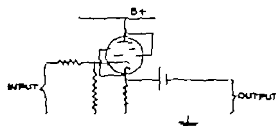


Fig. 3. Diagram of electrical circuit for high impedance.

from a neck vein, and a No. 6 Goodale catheter was passed from the femoral artery retrograde into the left ventricle. The cardiac output was measured by the Fick method. Hydrogen-saturated blood was injected at successively slower rates into an external jugular vein until it could just be detected by the electrode in the pulmonary artery. Similar injections were made into the left ventricle until hydrogen could just be detected by the femoral electrode.

Results

Detection of shunts in patients. The hydrogen-platinum system detected a left-to-right shunt in every instance in which the dye technique indicated the presence of this shunt. Typical curves are shown in Figs. 5 through 8. In 4 patients with smaller shunts (less than 0.5 times the systemic blood flow) the oxygen method gave equivocal or negative results. The hydrogen-platinum system did not detect a left-to-right shunt in any of the patients when the dye method failed to indicate its presence.

In 2 of the 3 patients with right-to-left shunts the hydrogen-platinum and the dye systems correctly detected the site of the right-to-left shunt. In the third, a patient with pulmonary stenosis and atrial septal defect, the dye and oxygen methods detected a small shunt (less than 15 per cent of the systemic venous return), although the hydrogen-platinum system failed to detect it. In this case, however, manual injection of 15 c.c. of blood into a No. 5 catheter was necessarily slow. Typical curves obtained with the hydrogen-platinum system are shown in Fig. 9.

Detection of valvular regurgitation was readily accomplished. Blood or saline previously exposed to hydrogen was injected into a catheter which was placed in the chamber immediately downstream from the valve. Regurgitant blood was detected with the platinum-tipped catheter in the immediate upstream chamber. A typical curve is shown in Fig. 10.

Results of the experiments performed on the 5 dogs with subclavian-pulmonary arterial anastomoses are shown in Table I. In each case the hydrogen-platinum system clearly detected the shunt earlier than did the other two methods and before the appearance of the murmur. No attempt was made to quantitate the shunt by the

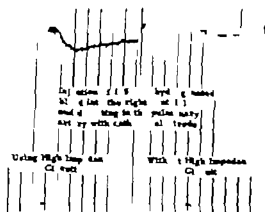


Fig. 4. Successive injections of hydrogen-saturated blood to an anesthetized dog, indicating curve obtained with and without the high-impedance circuit. Detection is indicated by deviation of electrode line from base line.



Fig. 5. Typical curve obtained in a patient without a shunt. The nosepiece used to detect the point of inhalation may be constructed of platinum or be rhodium plated. Oxidation potential and pulmonary arterial pressure curves were obtained from the same catheter.

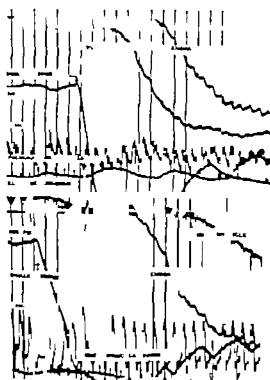


Fig 6 Curves obtained in a patient with patent ductus The change in oxidation potential is 3 seconds after inhalation of hydrogen in the pulmonary artery and 11 5 seconds in the right ventricle A rhodium nosepiece was employed

hydrogen platinum system but calculations were obtained after further deflation of the cuff permitted a great enough shunt to give positive results from the dye curves and the oxygen method (Table I)

The results of injection of hydrogenated blood into the external jugular vein and detection with an electrode catheter in the pulmonary artery indicate that as little as 2 c c injected at the rate of 13 c c per minute with a cardiac output of 3 L per minute gave a clear signal (Fig 11) Injection into the left ventricle of 3 c c of hydrogen saturated blood at the rate of 43 c c per minute with a cardiac output of 3 L per minute gave a clear signal from the electrode catheter in the femoral artery (Fig 12)

Discussion

The hydrogen platinum system has proved to be a reliable simple and accurate method for the detection and localization of small left to right shunts The technique can be repeated as frequently as necessary at the catheterization table without the withdrawal of samples of blood for dye curves or the insertion of multiple catheters Although this technique affords no known method for quantitation removal of samples through the same catheter from the pulmonary artery and vena cava for analysis of oxygen content will allow estimation of the size of the shunt The extreme sensitivity of the method however serves as a disadvantage in the presence of large shunts when valvular regurgitation is likely to occur Small amounts of hydrogen labeled blood which appear early in the right heart are



Fig 7 Curves obtained in patient with entricular septal defect with left to-right shunt which is indicated by the late appearance of change in oxidation potential in the right atrium as compared to the right ventricle A platinum electrode nosepiece was used for the signal of inhalation of hydrogen in recording the curv from the right entricle and interruption of the electrocardiogram was used for the other tw curves

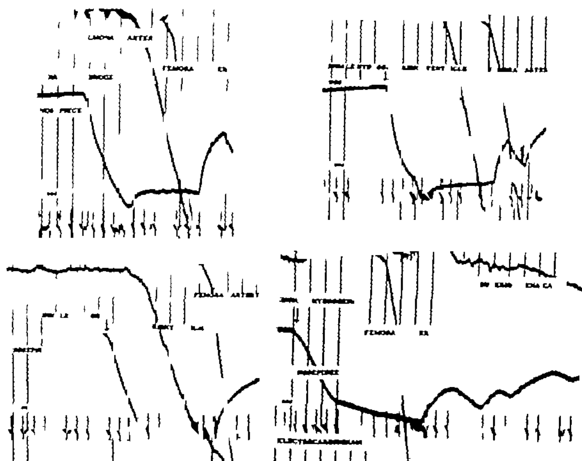


Fig. 8. Curves obtained in a patient with atrial septal defect. A rhodium nosepiece was employed.

detectable in the chamber immediately upstream from a regurgitant valve. In the present study the dye method usually presented the same problem and the oxygen method proved more reliable.

Experience with detection of right to left shunts in this investigation is limited. It is apparent, however, that with larger shunts (greater than 20 per cent of the systemic venous return) localization is readily obtained with the hydrogen platinum system. With smaller right-to-left shunts more *rapid injections should prove helpful. The* low solubility of hydrogen in saline or blood is disadvantageous; the labeling is not so massive as that obtained in the lung after inhalation of hydrogen. The hydrogen platinum system has the advantage of an unequivocal response. We have never detected hydrogen-labeled blood passing through the lungs of experimental animals by a platinum electrode in the left atrium or left ventricle or in exhaled air, nor have we detected it in human subjects without right to left shunts by an electrode in the femoral artery after injection was made into the right heart.

The relative sensitivity of the hydrogen platinum system is indicated by the studies with subclavian pulmonary arterial anastomoses. The oxygen method appeared to be more sensitive than previous experience in studies on congenital heart disease in this laboratory would suggest. However, in this study the samples for analysis of oxygen content were removed from both catheters simultaneously, without their manipulation, in anesthetized animals. Additionally, the quantity of the shunt could not be accurately gauged by the stepwise deflation of the cuff about the subclavian artery.

The modification of the Clark electrical circuit offers the advantage of representing the oxidation potential more adequately, independent of the size of the platinum

electrode Even with this more adequate registration of the natural logarithmic relationship of concentration to potential quantitation of the hydrogen concentration and hence the size of the shunt is not readily accomplished

Summary

A modification of the Clark hydrogen platinum system is described employing a high impedance system platinum electrode catheters and stylets for Cournand or Henry needles Typical curve which illustrate the localization of left to right and right to left shunts are presented Valvular regurgitation is readily detected The advantages of the method are the simplicity and reliability of the detection

Table I Summary of results obtained by stepwise deflation of a Jacobson cuff placed about a subclavian artery which had been anastomosed to the pulmonary artery

Cubic centimeters moved from cuff	H	Dye	O	Murmur
Dog No 1				
Occluded	0	0	0	0
0 10	+	0	0	0
0 15	+	0	0	0
0 20	+	0	0	Systolic component
0 25	+	+ 1 × PBF	+ 2 × PBF	Systolic and diastolic
Dog No 2				
0 05	+	0	0	0
0 10	+	0	0	Systolic component
0 15	+	+ 02 × PBF	+ 0 × PBF	Systolic component
Dog No 3				
0 05	0	0	0	0
0 10	+	0	0	0
0 15	+	0	0	0
0 20	+	+ 09 × PBF	+ 08 × PBF	0
Dog No 4				
0 05	0	0	0	0
0 10	+	0	0	0
0 15	+	+ 02 × PBF	0	0
0 20	+	+	0	0
All fluid removed	+	+ 15 × PBF	0	0
Dog No 5				
0 05	0	0	0	0
0 10	+	0	0	0
0 15	+	+ 4 × PBF	0	0
0 20	+	+	+ 5 × PBF	Systolic component

Abbr [illegible] d cated by [illegible] indicated by pl [illegible] Th [illegible] [illegible] below the [illegible] blood flow

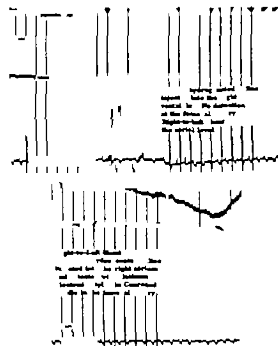


Fig 9 Curve obtained in patient with pulmonary stenosis and right-to-left shunt at the atrial level Hydrogenated saline gave signal at the femoral artery indicated by deviation from the base line only when injected at the atrial level or upstream but failed when injected into the right ventricle or pulmonary artery No change in oxidation potential was seen in the platinum nosepiece

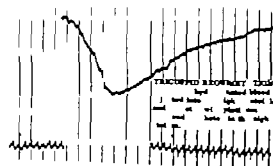


Fig 10 Curve showing detection of tricuspid regurgitation by means of regular catheter for injection and platinum electrode catheter for detection The signal is indicated by the deviation of the right atrial electrode catheter line from the base line

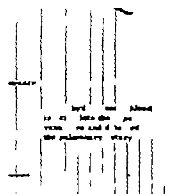


Fig 11 Curve showing detection of change in oxidation potential in pulmonary artery when 2 c.c. of hydrogenated blood was injected at rate of 13 c.c. min into neck vein of a dog with cardiac output of 3 L min

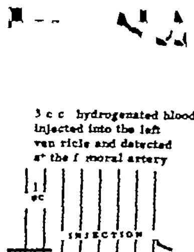


Fig 12 Curve howing detection of change in oxidation potential in the femoral artery of a dog when 3 c of hydrogenated blood was injected into the left entricle at a rate of 43 c.c./min The cardiac output as 3 L min

and localization of small shunts by means of a single intracardiac catheter The disadvantages of the method are its extreme sensitivity which complicates evaluation of valvular regurgitation and the lack of quantitation of the shunt volume

Addendum

Recently one of the authors (E S H) devised a circuit that registers hydrogen as a linear function of its concentration at a platinum electrode in vitro and in simple in vivo experiments By this method the aortic blood varies from 30 to 50 per cent saturated with hydrogen with various inhalations of 100 per cent hydrogen

We express appreciation to Mr Dewey Paulet, jeweler and Mr H H Schmidt jeweler manufacturer for assistance with royal metals and to Superior Tubing Co Norristown Pa for the stainless steel needle tubing

REFERENCES

1 Morrow A G Sanders R J and Braunwald E The nitrous oxide test An improved method for the detection of left-to-right shunts Circulation 17 2 1958
2 Sanders P J Use of radioactive gas (Kr⁸⁵) in diagnosis of cardiac shunts Proc Soc Exper Biol & Med 97 1 1958
3 Case R B Hurley H W Keating R P Keating P Sach H L and Loeffler E E Detection of circulatory shunts by use of a radioactive gas Proc Soc Exper Biol & Med 97 4 1958
4 Clark L Jr and Bargeron L M Jr Detection and direct recording of left-to-right shunts with the hydrogen electrode catheter Surgery 46 1 1959
5 Swan H J C Zapata Diaz J and Wood E H Dye-dilution curves in cyanotic congenital heart disease Circulation 8 6 1953
6 Hyman A L Levy L H Bagnetto R and Ordway N Application of newer diagnostic methods in congenital heart disease New Orleans M & S J 103 1 1950
7 Hyman A L Hyman E S Quiroz A C and Gantt J R Comparison of the platinum rhodium hydrogen electrode and oxygen methods in detecting shunts S Forum 11 1960 (In press)

Experimental and laboratory reports

Analysis of heart motion with ultrasonic Doppler method and its clinical application

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Ultrasound has been used in industry to detect flaws in metal and to sound the depth of the sea a good transmittance and sharp direction of ultrasound in a given substance can attest such utilization Quite naturally too ultrasound has been used to study the inner aspects of the human body It was first employed in detecting tumors and gallstones and has also been applied to the heart by Keidel Edler and Hertz [illegible] Wild and others

In the present study the ultrasonic Doppler method was adopted It features a device to represent the movements of the target to be examined and enables one to detect the time in which movements of the valves occur

Method

A Principle

1 TRANSMITTANCE DIRECTION AND REFLECTION IN THE BODY OF THE ULTRASOUND Ultrasound is a sonic wave with a frequency above the audible range (16 c p s 16 000 c p s on an average) The propagation of ultrasound follows the Huygens principle as in the case of an audible sound When an ultrasound which has a wave length λ is sent in one direction from a circular plane source having diameter d 90 per cent of the energy of the ultrasound is included in solid angle θ which is determined by the following formula[illegible]

$$\sin \theta = 1.22 \lambda/d$$

where θ is small since λ of the ultrasound is small i e the energy of the ultrasound is sent mostly in one direction with little divergence Thus it is understood that the ultrasound possesses a sharp direction The ultrasound has a straight propagation into the living body as does X ray It can be used in examining those targets in the path of its transmission

When the ultrasound is transmitted into the living body from its surface a part of the transmission is reflected from the boundary between two living tissues which possess different sound impedances

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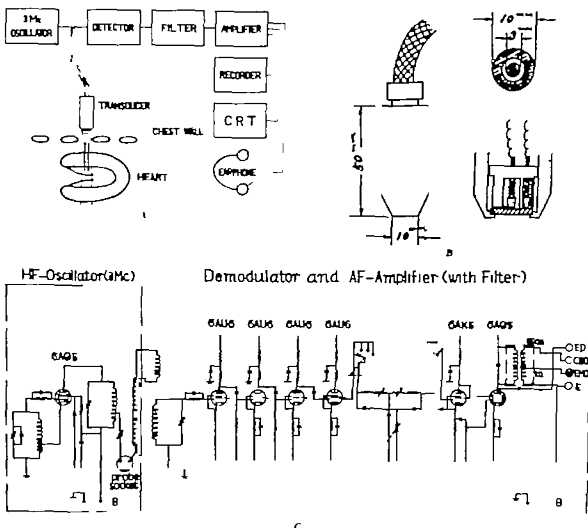


Fig 1 Instrument A Schematic block diagram B Transducer and its holder C Circuit

For instance in the heart the ultrasound is partially reflected from the outer surface and inner surface of the heart wall from the valves and from the surface of both sides of the septum etc Accordingly it is possible to obtain information about the inside of the heart (e g the movements of the valves) which would be denied to other methods such as x ray

2 PRINCIPLE OF THE ULTRASONIC DOPPLER METHOD When the continuous beam is transmitted from the chest wall to the heart and is reflected from the heart wall and valves it undergoes Doppler effect subject to the movements of the heart[11] When this reflected wave is detected together with the direct wave a beat appears the frequency of which is (f_d)

$$f_d = 2\,\mu/\lambda$$

Here μ represents the velocity component of the target in the direction of the ultrasonic beam and λ is the wave length of the ultrasound transmitted in the living body The frequency of the beat is proportional to the velocity component of the target The present authors have employed an amplifier for observance of this beat in an attempt to get information about the heart wall valves etc When the target is kept still i e strictly speaking when the velocity of the target does not possess a component in the same direction as the ultrasonic beam no beat occurs Hence this method is considered to be closely related with the movements of the target examined

B Instrument Fig 1 describes the schema of the apparatus[11] used The high

frequency oscillator employed was of 1.2 watts the frequency being 3 megacycles per second. A disc of barium titanate 1 cm. in diameter was used as the electrosonic transducer. The disc was divided into two parts being a concentric circle. The inner and outer parts were used for sending and detection respectively (Fig. 1,B). In the area for detection the direct wave as well as the reflected waves were detected electrically or mechanically; a beat develops between these two waves.

The calculated value of the power of the ultrasound was about 20-30 milliwatts per square centimeter. Cavitation which causes influential physiologic effects on the living tissue develops mostly at over 300 milliwatts per square centimeter. Therefore, in the present study, the intensity of ultrasound employed for a few minutes seems to be free from any untoward side effects. The aforesaid *θ* was about 4 degrees. An ordinary type of pentode grid demodulator was used as a detector. The amplification of the low frequency amplifier was 60-80 decibels. As the filter, a low pass (cut-off frequency 200 c.p.s.) filter and a band pass filter of 500-1,000 c.p.s. were employed.

The Doppler signal was recorded by means of an electromagnetic oscillograph under the control with an earphone and/or a Braun tube. The paper speed was 20-30 cm. per second. We usually recorded the Doppler signal simultaneously with the ECG and PCG and made comparative study of these. Fig. 1,C shows the diagram of the apparatus employed.

Results and discussion

Part I. The kinds of Doppler signal due to heart movements

1. THE KINDS OF DOPPLER SIGNAL DUE TO HUMAN HEART. When this method was applied to a human body, a transducer was closely attached to the precordial area. Here fluid paraffin was employed for the removal of the air between the skin and the transducer so as to give a good contact. The Doppler signal can be obtained in any area in which the heart is attached to the chest wall. But when transmission to the target is carried out through the lung, the ultrasound is absorbed by the air in the lung, and it is difficult to obtain the Doppler signal with the intensity of ultrasound used in the present study. Occasionally, it is difficult to obtain the recording in an athletic human body which has a short and wide thorax. Moreover, ultrasound does not transmit through bone tissues.

The Doppler signal thus obtained was classified into the following two kinds in terms of frequency[1, 2]: (a) low frequency signal of less than 500 c.p.s., mostly 100-200 c.p.s., and (b) high frequency signal of about 1,000 c.p.s. In the present study

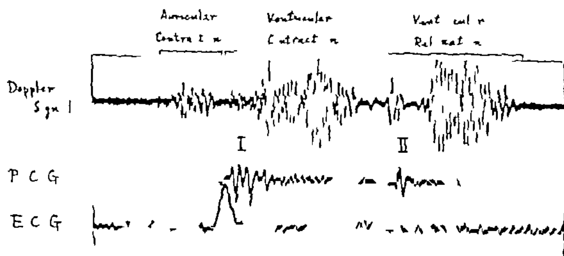


Fig. 2. Ultrasonic Doppler signal of low frequency (in the fourth left intercostal space at the parasternal line) related to the movement of the heart wall.

a filter was generally used to record these two signals separately

2 THE LOW FREQUENCY SIGNAL The low frequency signal obtained in healthy subjects is shown in Fig 2 When compared with the ECG and the PCG which were recorded concurrently this signal begins to appear within almost 0 04 0 09 second



Fig 3 High frequency Doppler signal related to the movement of the valve (exposed dog heart) *Top* Tricuspid valve *Bottom* Pulmonic valve

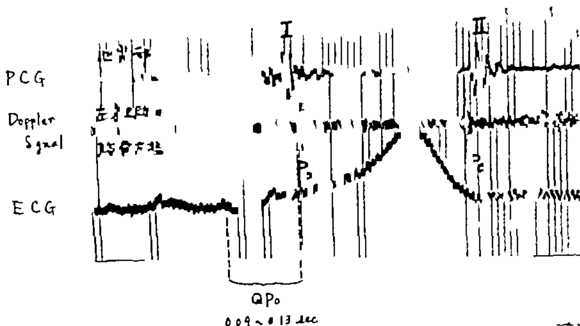


Fig 4 Ultrasonic Doppler signal of high frequency related to the pulmonic valve P Opening P Closing The end of P coincides with the beginning of the second heart sound (S T 30 ear-old healthy man)

after the beginning of the QRS nearly at the same time as the beginning of the first heart sound

The first half of the low frequency signal lasts almost until the summit of the T The latter half begins almost at the same time as the second heart sound and lasts for about 0 3 second It is reasonable to consider that this low frequency signal is related to the movements of the heart wall and that its first and latter halves are due to the movement in systole and diastole respectively The site for low frequency signal in the present study was generally represented by the fourth intercostal space on the left parasternal line

Besides the aforementioned low frequency signal a low frequency signal appears at the time corresponding to the P Q (Fig 2) This low frequency signal begins 0 08 0 13 second after the beginning of the P (mostly in 0 10 0 11 second) and lasts for 0 07 0 12 second The time of the beginning and the duration of this low frequency signal are similar to the time of beginning and the duration of the auricular sound * This signal is considered to indicate the movements of the heart wall which accompany an auricular contraction

3 THE HIGH FREQUENCY SIGNAL The high frequency signal appears subsequent to the QRS as well as nearly at the end of the T and it lasts for a short time (Figs 4 and 6) With regard to its frequency the target is understood to move with a speed several times faster than that of the target of the aforesaid low frequency signal Considering this high speed and the time of appearance it is understood that the target examined must be a valve (tendon papillary muscles etc may also be referable) The finding that the time of appearance of the high frequency signal is slightly different in the basal area from that in the apical area can be reasonably interpreted in accordance with the difference of the time of the movements in the semilunar valve from that in the atrioventricular valve

4 EXPERIMENT IN EXPOSED DOG HEART An attempt was made to confirm that the high frequency signal is related to valvular movements A transducer was applied on the exposed surface of the dog heart in order to ascertain where the high frequency signal could be obtained [11] and we found that the signal could be obtained in the vicinity of (a) the tricuspid valve (b) the mitral valve and (c) the pulmonic valve when the ultrasonic beam was sent toward these valves

In the vicinity of the tricuspid valve the

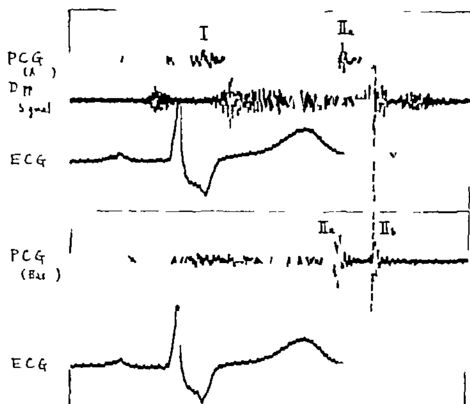


Fig 5 Delayed closing of the pulmonic valv in RBBB Second basal sound is reduplicated Its earlier component IIa is interpreted as being due to the aortic valv its later component IIb due to the pulmonic valv The latter does not appear in the apical region Doppler signal Pc has been obtained in the second intercostal pace t the left sternal edge. Its end coincides as expected with the beginning of IIb (H A 30-year old man)

high frequency signal begins 0 04 to 0 05 second after the beginning of the QRS and 0 05 second after the end of the T (Fig 3 *top*) The time of appearance is about the same in the vicinity of the mitral valve In the vicinity of the pulmonic valve the high frequency signal appears 0 09 second after the beginning of the QRS and nearly at the end of the T (Fig 3 *bottom*) Thus in regard to early systole the high frequency signal obtained in the vicinity of the tricuspid valve appears 0 04 second earlier than that in the vicinity of the pulmonic valve On the contrary in regard to nearly the end of the T the high frequency signal obtained in the vicinity of the pulmonic valve appear 0 05 second earlier than that in the vicinity of the tricuspid valve When the site and time for the development are considered such a high frequency signal seems to be related to the movements of the related valves probably inclusive of chordae tendineae and papillary muscles and to denote the time of movements It is understood that the time intervals between the signal of the pulmonic valve and that of the tricuspid valve in early systole and at nearly the end of the T signify the duration of isometric contraction and the duration of isometric relaxation respectively

In so far as the time of development and the frequency are concerned the high Doppler signals obtained on the human chest wall correspond to those of the aforesaid dog Therefore this seems to confirm that the high frequency signal from a human being indicates the time of valvular movements

Part II The high frequency Doppler signal due to valvular movements in a human being and its clinical application

1 THE HIGH FREQUENCY DOPPLER SIGNAL DUE TO VALVULAR MOVEMENTS The high frequency Doppler signal in a human being[1] [4] which is considered to be due to

the movements of the semilunar valves is most clearly recorded exclusively with the transducer on the left sternal edge in the third intercostal space, sometimes in the second or fourth intercostal spaces (Fig. 4). On the basis of the findings in cases of bundle branch block or reduplicated basal second sound as mentioned later on, it is concluded that the Doppler signal due to the aortic valve is obtained on the left sternal edge in the third or fourth intercostal space, and the Doppler signal due to the pulmonic valve is obtained on the left sternal edge in the third or second intercostal space. A semilunar valve is so small a target that it needs a limited site of the transducer and a limited direction of the ultrasonic beam.

The Doppler signal due to the opening of a semilunar valve in a healthy human being appears 0.09–0.14 second after the beginning of the QRS; the signal due to the closing of a semilunar valve appears just before the second heart sound and its termination coincides with the beginning of the second heart sound (Figs. 4 and 5).

According to this finding, the second heart sound develops almost simultaneously with the completion of the closing of a valve, that is, the second heart sound seems not to be caused by the movements of the valves themselves but by the tension or vibration of the related valves and their adjacent tissues due to impulses which develop directly after the closing.

Strictly speaking, it is frequently difficult to define in a human being whether the Doppler signal due to a semilunar valve is caused by the pulmonic valve or by the aortic valve. Mostly both valves seem to move simultaneously. But in some cases the two signals due to these valves can be differentiated as to time and site. Then the opening of the aortic valve (Ao) begins 0.09–0.14 second (average 0.107 second, 7 cases) after the beginning of the QRS, and the opening of the pulmonic valve (Po) begins 0.09–0.13 second (0.106 second, 25 cases) after (Table I). But in cases in which both signals are recorded, Po precedes Ao by 0.02 second or less. Moreover, the signal due to either of these valves is obviously differentiated in cases with bundle branch block and cases with a reduplicated or split second heart sound. As soon as the signal for the closing of the aortic valve or pulmonic valve (Ac or Pc respectively) terminates, the respective component of the second heart sound begins (Fig. 5).

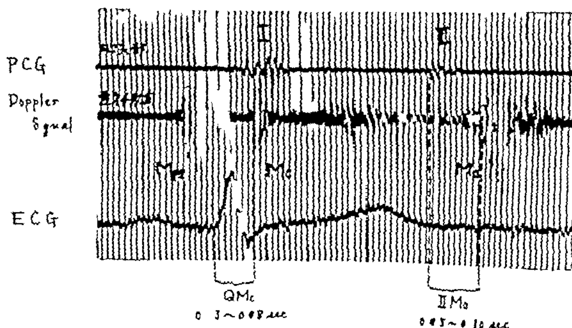


Fig. 6 Ultrasonic Doppler signal of high frequency interpreted to be related to the mitral valve. Mc: Closing, Mo: Opening (S. N., a 3?-year-old man)

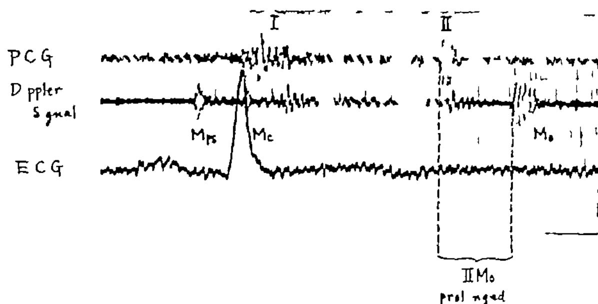


Fig 7 Delayed opening of the mitral valve in myocardial change (T S 52 year-old woman with hypertension)

The Doppler signals which seem to be related to the atrioventricular valve especially those due to the mitral valve are most likely to be detected on the left parasternal line in the fourth intercostal space

Of these signals the signal due to the closing of the mitral valve (Mc) in a healthy human being begins 0 03 0 08 second (average 0 054 second 76 cases) after the beginning of the QRS (Table II) the interval between the Mc and the QRS varies with different pathologic conditions (Fig 6)

The signal due to the opening of the mitral valve (Mo) in a healthy human being begins 0 05 0 10 second (0 069 second 81 cases) mostly 0 06 0 08 second (Table III) after the closing of the semilunar valve is completed i e the beginning of the second heart sound (II) The signal for either the closing or opening requires about 0 02 0 04 second

Another high frequency signal (Mps) appears at the time which corresponds to the P Q (Fig 6) It begins approximately at the same time as a low frequency signal which appears at the interval corresponding to the P-Q and the auricular sound [19,20] i e 0 10 to 0 13 second after the beginning of the P In cases in which there is complete atrioventricular block Mps accompanies the P independently of the QRS It does not appear in cases in which there is auricular fibrillation When these findings are considered it is assumed that Mps is caused by valvular movements which are due to an inflow of the blood into the ventricle at the time of auricular contraction

The Doppler signal which is due to the tricuspid valve is obtained on the left lower sternal edge That signal is frequently difficult to differentiate from the signal due to the mitral valve as to time and site Both valves seem to open almost simultaneously But in some cases a signal (Tc) which can be defined as obviously being due to the tricuspid valve occurs 0 04 0 05 second (average 0 043 second 9 cases) after the beginning of the QRS (Table II) At that time it precedes the opening of the mitral valve by 0 01 0 02 second

In cases in which there is a great interval between the time of the right and left ventricular contractions e g bundle branch block, the respective signals due to these two valves can obviously be differentiated from each other

Thus the time of the opening and closing of the valves if detected will lead one to determine the duration of isometric contraction isometric relaxation etc Of course it is possible to measure the isometric relaxation on the left side and right

Table I *Time of opening of semilunar valves*

Second	*QAo* (Number of cases)	*QP* (Number of cases)
0 09	2	5
0 10	2	7
0 11	1	8
0 12	1	4
0 13	0	1
0 14	1	0
	7	25

Table II *Time of closing of atrioventricular valves*

Second	*QMc* (Number of cases)	*QT* (Number of cases)
0 03	1	0
0 04	14	6
0 05	28	3
0 06	20	0
0 07	10	0
0 08	3	0
	76	9

Table III *Duration of isometric relaxation (IIMo)*

Second	*IIM* (Number of cases)
0 05	10
0 06	23
0 07	28
0 08	9
0 09	9
0 10	2
	81

side separately under the conditions wherein the opening and closing of the pulmonic valve (Po Pc) and of the tricuspid valve (To Tc) can be differentiated from the opening and closing of the aortic valve (Ao Ac) and the mitral valve (Mo Mc) Here it must be admitted that since the end of the closing of the semilunar valves coincides with the beginning of the second heart sound the duration from the beginning of the second heart sound (II) to the beginning of Mo (To) is used as the duration of isometric relaxation instead of the duration from the beginning of the closing of the semilunar valves to the beginning of Mo for the convenience of recording in the following description

The duration of isometric contraction in healthy persons is 0 03 0 08 second The duration of isometric relaxation (IIMo) in most cases is 0 06 to 0 08 second (Table III) cases of bradycardia show mostly a trend of slight prolongation of isometric relaxation

2 FINDINGS IN PATHOLOGIC CASES The time of valvular movements detected by the present method varies according to different pathologic conditions above all the time of opening of the mitral valve (Mo) is especially variable and results in marked changes in the duration of isometric relaxation The findings so far obtained of the time of valvular movements are presented below

a Myocardial changes (coronary sclerosis and hypertensive heart disease) Cases in which there are ST T changes in

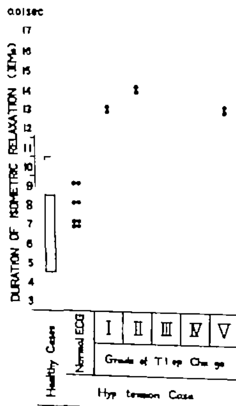


Fig 8 Relationship between duration of isometric relaxation and grade of T loop change in cases of hypertension and left ventricular strain pattern

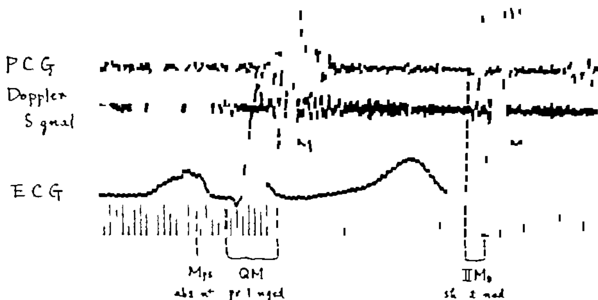


Fig 9 Movement of the mitral valve in mitral stenosis. *Mps* is absent. *M* is slightly delayed. *IIM* is shortened. The opening snap begins while M develops (S D 38 year-old man with mitral stenosis.)

the left precordial leads (with a few exceptional cases) show a markedly delayed opening of the mitral valve over the end of the T (Fig 7) The isometric relaxation is over 0 10 second mostly 0 12 0 14 second and occasionally reaches 0 18 second The mechanism of such delay has not been clarified But the delay suggests that a certain factor or factors disturbs a smooth shift of the myocardium from mechanical systole to mechanical diastole Electrocardiographically a delayed repolarization of the myocardium especially of the outer layer of the myocardium may be interpreted as playing a great role in the mechanism of ST T changes The existence of a relationship between an electrical delay and a mechanical delay is suggested leaving a problem to be pursued in the future

b Hypertension Generally cases of hypertension show a delay in Mo But there is no close relationship between the grade of hypertension and the grade of delay Cases in which there is a normal ECG show mostly a slighter grade of delay than the aforesaid cases in which there are ST T changes The severity of the left ventricular strain pattern has been classified by us on a vectorcardiographic basis into five grades[22,23] According to this classification it seems that the severer the grade of ST T changes the longer the duration of isometric relaxation (Fig 8) However some cases in which there is a normal ECG show also a delay occasionally They even show marked changes This seems to afford promise of an early detection of myocardial changes

c Mitral valvular disease In cases of mitral stenosis and mitral stenosis and regurgitation without auricular fibrillation generally no Mps develops in the presence of the P (Fig 9) The disappearance of the Mps was observed in all of 29 cases of stenosis and in all but 3 of 18 cases of stenosis and regurgitation This result seems to shed a bright light on the facilitation of diagnosis The mechanism of the disappearance of the Mps has been left obscure but a possible interpretation is that the movements of the mitral valve may be limited by the hardness of the valve

Other representative findings in mitral valvular disease are a delayed closing of the mitral valve and an early development of the opening of the mitral valve i e a trend of prolongation of QMc and a shortening of IIMo (Fig 9)

The prolongation of QMc is comparable to the PCG finding in which the first heart

sound develops late in cases of mitral valvular disease[20, 4]. Its mechanism may be referable to an insufficient ventricular filling, an elevated left auricular pressure and a delay in elevation of the left ventricular pressure due to a regurgitation.

Elevation of the left auricular pressure is suggested as a factor which induces early opening of the mitral valve. In this study an attempt was made to find a relationship between IIMo duration and the ECG abnormalities (Table IV). In cases of mitral stenosis, those in which right ventricular hypertrophy or a trend toward it is shown on the ECG reveal a more marked shortening of IIMo than do those cases in which QRS is normal on the ECG. Both these two abnormal findings seem related to a marked elevation of left auricular pressure. On the other hand, cases of mitral stenosis and regurgitation show a trend of marked shortening of IIMo even in the presence of normal findings on the ECG. This may be attributable to a specific elevation of left auricular pressure at the final stage of systole due to regurgitation or attributable to an apparently normal ECG because of a mutual cancellation in the ECG of the influence of left and right ventricular hypertrophy.

A study of the opening of the mitral valve made in comparison with the opening snap reveals that the latter seems to begin in correspondence with the middle of the duration of the former (Mo) (Fig. 9).

During the present study there was a IIMo of 0.04 second in one case and after commissurotomy it was 0.06 second.

A trend in the shortening of IIMo is also observed in cases of congestive heart failure of other etiology.

Here it must be added that in a case of mitral stenosis with right ventricular hypertrophy a delay in the opening of the tricuspid valve, i.e., a prolongation of the IITo to 0.10 second, was seen.

Cases of auricular fibrillation tend to demonstrate the effects of auricular fibrillation[1, 3] markedly. QMc is related to the preceding R-R. A general trend is that the shorter the latter, the longer the QMc, that is, the longer the preceding R-R, the more delayed is the closing of the mitral valve. Eliakim and others[7] stated the same opinion on the basis of heart catheterization. IIMo is not so much shortened in cases of auricular fibrillation. Its relationship with the preceding R-R is not clearly detected. However, it is likely that a markedly short preceding R-R is accompanied by a more or less short IIMo.

d. Kidney diseases. Cases of nephritis show a delayed opening of the mitral valve and a prolongation of isometric relaxation. Such abnormalities are generally marked in cases of impaired renal

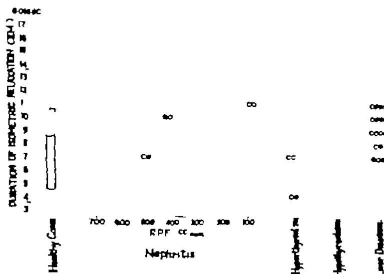


Fig. 10. Duration of isometric relaxation under various conditions. The white circles indicate cases in which the ECG was normal, and the black circles indicate cases in which myocardial change was shown in the ECG.

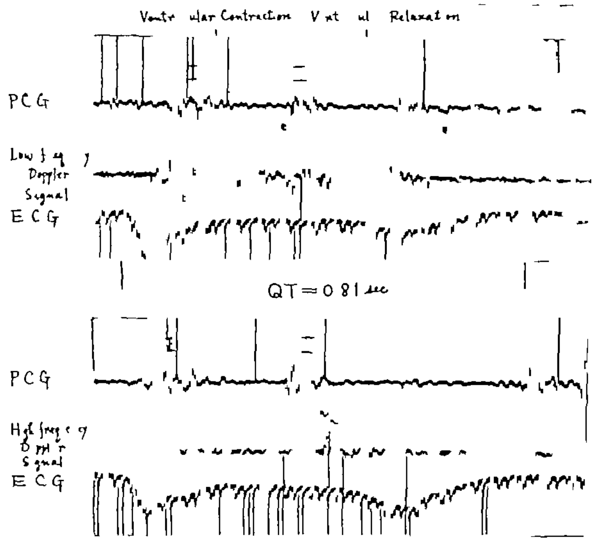


Fig 11 Findings in case in which there was markedly prolonged Q T *Top* Low frequency signal *Bottom* High frequency signal (mitral valve) (M Y a 31 year-old man with angina necroticans)

function As shown in Fig 10 even cases in which the ECG is normal demonstrate a prolongation of isometric relaxation This seems significant in an early diagnosis of myocardial involvement Here it must be admitted that such prolongation is due to an early development of the second heart sound in a few cases

e Dysfunction of thyroid gland Ten cases of hyperthyroidism without myocardial change in the ECG showed no marked changes in the opening time of the mitral valve (Fig 10) Five cases of hypothyroidism showed a IIMo duration of 0 16 0 13 0 11 0 10 and 0 08 second (Fig 10) the fourth case (0 10 second) showed a Q T prolongation and in the other 4 cases there were ST T changes In the third case edema disappeared after the administration of a thyroid preparation the ECG returned to normal and IIMo became 0 06 second

f Liver disease Of 20 cases of cirrhosis of the liver or chronic hepatitis IIMo duration was 0 05 0 09 second in 11 cases and 0 10 0 14 second in 9 cases (Fig 10) Thus an obvious prolongation is observed in about half of the cases studied Of the latter 9 cases the 4 cases which showed a IIMo of 0 10 second had the second heart sound appearing 0 04 0 08 second before the end of the T It is understood that in these cases a prolongation of isometric relaxation is due to early develop

ment of the closing of the semilunar valves rather than to a delay in the opening of the mitral valve in regard to the end of the T. The other 5 cases showed a IIMo of 0.11-0.14 second and revealed mostly a delayed opening of the mitral valve.

g. Cases with marked Q-T prolongation. It is interesting to note what changes in mechanical movements are found in cases which show a marked prolongation in an electrical phenomenon. Fig. 11 shows an example of the final stage of angina necroticans in which Q-T covers 0.81 second. The low frequency Doppler signal which denotes the movements of the heart wall in contraction begins 0.07 second after the beginning of the QRS and ends 0.34 second after the beginning of the QRS (Fig. 11 *top*). Even that in relaxation ends nearly at the peak of the T. Thus it is suggested that in such cases there would be some parts of the myocardium in which repolarization is locally delayed because of marked myocardial damages. Hence, even when relaxation is almost finished in the greater part of the myocardium, a large abnormal T persists because of such localized delayed repolarization.

The aforementioned case, as shown in Fig. 11 *bottom*, reveals an extremely earlier development of the opening of the mitral valve than the end of the T.

In cases such as those of hypopotassemia *in which the U wave appears superposed on the end of the T the opening of the* mitral valve, as well as the second heart sound, appears earlier.

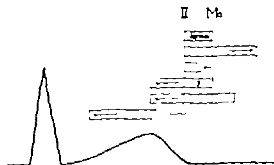


Fig. 12. Modes of time relationship between opening of the mitral valve, second heart sound, and the end of T. *1*. A delayed opening of the mitral valve. *2*. An early development of the opening of the mitral valve. *3*. An early development of the second heart sound. *4*. Coexistence of *1* and *3*. *5*. Marked Hegglin syndrome.

The correlationship in terms of time between the opening of the mitral valve, closing of the semilunar valves, and electrical events seems to be very much complicated. It is detailed as follows (Fig. 12): (1) delay in the opening of the mitral valve as found in coronary sclerosis, hypertensive heart, etc.; (2) early development of the opening of the mitral valve as found in mitral stenosis and congestive heart failure; (3) early development of the closing of the semilunar valves (second heart sound), i.e., Hegglin syndrome[11]; (4) early development of the second heart sound and delayed opening of the mitral valve; (5) severe cases of Hegglin syndrome which show a markedly early development of the opening of the mitral valve.

Table IV. Relationship between ECG and duration of isometric relaxation in cases of mitral stenosis or mitral stenosis and regurgitation (number of cases)

		IIM (Second)						
		0.02	0.03	0.04	0.05	0.06	0.07	0.08
MS	Cases with abnormal ECG	3	9	4	1	5	0	0
(29 cases)	Cases with normal ECG	0	0	3	2	2	0	0
MSI	Cases with abnormal ECG		2	1	2	2	0	0
(18 cases)	Cases with normal ECG	2	0	2	0	3	1	1

MS: Mitral stenosis. MSI: Mitral stenosis and regurgitation.

Table V Time of valvular movements in cases of RBBB and cases of LBBB

	RBBB		LBBB	
	Number of cases	Average (range seconds)	Number of cases	Average (range in seconds)
QMc	15	0 058 (0 04–0 09)	5	0 086 (0 07–0 11)
QTc	9	0 083 (0 07–0 10)	5	0 062 (0 05–0 09)
QAo	14	0 12 (0 10–0 14)	5	0 174 (0 16–0 20)
QPo	11	0 160 (0 14–0 17)	4	0 135 (0 12–0 16)
M Ao	14	0 066 (0 04–0 09)	5	0 090 (0 05–0 12)
T P	5	0 082 (0 07–0 09)	4	0 070 (0 06–0 10)
IIaM	15	0 113 (0 06–0 13)	3	0 137 (0 13–0 14)
IIpT	4	0 103 (0 08–0 12)	4	0 115 (0 10–0 13)

It is understood that the conversion phase from ventricular contraction to relaxation is to be discussed in reference to (1) its beginning i e the time of development of the second heart sound and (2) the duration of isometric relaxation

Suggested in regard to the determination of the length of isometric relaxation are the conditions of the myocardium itself such as are anticipated to be present in cases of myocardial changes and passive conditions such as an increased atrioventricular pressure difference which is considered in cases of mitral stenosis It is assumed that the above mentioned conditions may act simultaneously to determine the duration of isometric relaxation

b The time of valvular movements in bundle branch block The time of movements of each valve was detected in several cases of bundle branch block by the ultrasonic Doppler method The result is shown in Table V

Summary

1 The ultrasonic Doppler method has been used to obtain information on the movements of the heart

2 The time of development of valvular movements is determined a wide range of variation under various conditions is shown

3 In cases of coronary sclerosis hypertension etc the opening of the mitral valve is delayed revealing a prolonged duration of isometric relaxation The abnormalities develop prior to myocardial change in the ECG

4 In cases of mitral stenosis the closing of the mitral valve is delayed and the opening is quickened showing the shortening of isometric relaxation

5 In cases of mitral valvular disease with auricular fibrillation the shorter the preceding R R the more delayed is the closing of the mitral valve

6 Prolonged isometric relaxation develops even in cases of nephritis hypothyroidism liver disease etc

7 The time relationship between the opening of the mitral valve the closing of the semilunar valves and the end of the T wave is referable to the following modes (a) a delayed opening of the mitral valve (b) early development of the opening of the mitral valve (c) early development of the closing of the semilunar valves (Hegglin syndrome) (d) coexistence of (a) and (c) (e) early development of the opening of the mitral valve subsequent to early development of the closing of the semilunar valves in cases of marked Hegglin syndrome

REFERENCES

1 Wild J J and Reid J M Ultrasonic ranging speeds Cancer diagnosis Electronics 28 No 3 174 1955
2 Wild J J and Reid J M The effect of biological tissues on 15 M pulsed ultrasound J Acoust Soc Am 25 270 1953
3 Ludwig G D and Struthers F W Detecting gall stones with ultrasonic echoes Electronics 23 No 2 172 1950
4 Kikuchi Y Uchida K Tanaka R and Wagai T Early cancer diagnosis through ultrasonics J Acoust Soc Am 29 824 1957
5 Tanaka R Wagai T Kikuchi Y and Uchida K Choompa in Yoru Zogai nai shikkan no

*Translation of the J pa ese title is se tted by ban den by the present authors

Kenkyu [illegible] (On [illegible] cranial diseases with ultrasound II) J Jap Surg Soc 54 [illegible] 19[illegible]

6 Fukuda, T., Tanaka, R., and [illegible] T Choonpa no Shindan e no Oyo (Ultrasound applied in clinical diagnosis) J Jap [illegible] Soc 13 37 19[illegible]

7 Yamakawa, K. Fukutomo [illegible] Yoru Fukubu [illegible] no Kenkyu (A study on photographing intra abdominal organs with laparoscope) Lecture at the [illegible] Annual Meeting of the Gastroent Soc Jap 13 [illegible] 19[illegible]

8 Keidel W D Über eine neue Methode zur Registrierung der Volumenveränderungen des Herzens am Menschen, Ztschr Kreislaufforsch 39 25 19[illegible]0

9 Edler I and Hertz, C H The use of ultrasonic reflectoscope for the continuous recording of the movement of heart walls Kungl Fysiografiska Sall Lunds Forhandl [illegible] 24 [illegible] 1 1954

10 Edler I and Gustafson A Ultrasonic cardiogram in mitral stenosis Acta med scandinav 159 [illegible] 1957

11 Hertz C H, and Edler I Die Registrierung von Herzwandbewegungen mit Hilfe des Ultraschallimpuls verfahren, Acustica 6 [illegible] 1956

12 Wild J J Crawford H D and Reid J M Visualization of the excised human heart by means of reflected ultrasound or echography Am Heart J [illegible]-903 1957

13 Bugard P Les ultrasons Paris, 1948 Presses Universitaires de France

14 Hueter T F and Bolt R H Sonics New York, 1955 John Wiley & Sons Inc

15 Satomura S Ultrasonic Doppler method for the inspection of cardiac functions J Acoust Soc Am 29 1181 195[illegible]

16 Satomura, S Choonpa Doppler ho ni Yoru Shinzo-kino-kensa no Kenkyu I Genri II Sochi (A study on examining the heart with ultrasonics I Principle II Instrument) Jap Circul J 20 227 195[illegible]

17 Yoshida T Mori, M Nimura, Y Okumura M Hikita G Nakanishi K and Satomura S Choonpa Doppler ho ni Yoru Shinzo-kino-kensa no Kenkyu III Doppler ho no Shurui IV Rinsho-teki-oyo (A study on examining the heart with ultrasonics III Kinds of Doppler beats IV Clinical application) Jap Circul J 20 [illegible] 28 19[illegible]6

18 Yoshida T Mori, M Nimura Y Takagishi S and Nakanishi K Shinzo ni Okeru Choonpa-shindan ho no Oyo (Ultrasonics clinically applied in examining the heart) Saigo-rinsho 8 391 1959

19 Takagishi S [illegible] Doppler [illegible] J Osaka [illegible] (Japanese [illegible]) [illegible]

20 Yoshida T [illegible] Nimura Y Takagishi S and Nakanishi K [illegible] Yoru [illegible] to [illegible] cardiac function with ultrasonics in reference to heart sound [illegible] 1[illegible] 143 1[illegible]

21 Hikita G [illegible] K Okumura M Takagishi S Nimura Y Mori, M Yoshida T Yoshida M [illegible] S and Satomura S Choonpa Doppler-ho ni Yoru Shinzo-kino kensa no Kenkyu V Ben no Doppler-on ni Tsuite (A study on examining the heart with ultrasonics V Doppler beat due to valves) Jap Circul J 20 [illegible] 19[illegible]

22 Nimura, Y A vectorcardiographic study of left ventricular [illegible] pattern comparatively studied with ST T change of left bundle branch block and ventricular premature beat of right ventricular origin Am Heart J [illegible] 552 19[illegible]

23 Yoshida T [illegible] Nimura, Y [illegible] M Nakamura, K, Okumura M and Shirai J On vector cardiogram VII Clinical study on types of ST T change, Jap Circul J 19 198 195[illegible]

24 Nakanishi K Study on the valvular movement in mitral valvular disease by the ultrasonic Doppler method, Med J Osaka Univ (Japanese edition) 11 [illegible] 19[illegible]

25 Wells B The assessment of mitral stenosis by phonocardiography Brit Heart J 16 261 1954

26 [illegible] J J Diagnostic value of phonocardiography in mitral stenosis Mode of production of first heart sound Am J Med 19 [illegible] 195[illegible]

2[illegible] Yamamoto [illegible] Yamamoto T O[illegible] S and [illegible] K [illegible] of delay of [illegible] of the first sound in mitral stenosis Jap Circul J 19 127 1954

28 [illegible] H [illegible] S Kato [illegible] J Yamashita T Hara Y Hashimoto H [illegible] Y and [illegible] F Genesis of the first heart sound Viewed from hemodynamics and mechanical [illegible] Jap Circul J 21 170 1957

29 Rosenberg S [illegible] Hakim M and [illegible] F Relationship between electrical and mechanical events in total [illegible] A study of direct [illegible] pressure tracings Am Heart J 53 18 1957

30 Hegglin R Die Kombinierte [illegible] Herzinsuffizienz [illegible] Herzmuskelschwäche [illegible] 1104 1941

The experimental induction of myocardial infarction

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Myocardial infarction may be induced experimentally by ligating one of the coronary arteries or by embolization of a coronary artery with a foreign material such as liquapodium or glass beads. It is evident, however, that these methods do not correspond to the actual conditions under which myocardial infarction occurs in man. In man, myocardial infarction generally develops as a result of arteriosclerotic changes in the wall of the coronary arteries. In addition, functional factors such as myocardial stress, spasm of the coronary arteries, and biochemical changes play a role in the pathogenesis of myocardial infarction.

We have undertaken to produce experimental myocardial infarction in rabbits without resorting to the mechanical methods generally utilized to obstruct the supply of blood to cardiac muscle. Instead, those factors were utilized which are generally considered to contribute to the development of myocardial infarction in man.

Experimental method

Coronary atherosclerosis was induced in rabbits by the administration of cholesterol in the diet for 6 months according to the method of Anichkov. These cholesterol-fed animals were subjected to additional factors which, from the clinical point of view, were considered to contribute to the development of myocardial infarction. These additional factors included myocardial stress, altered blood coagulability, and coronary arterial spasm.

1. Twenty-two animals were made arteriosclerotic by feeding them cholesterol but were not subjected to any other influences considered to produce myocardial infarction.

2. Twenty-five cholesterol-fed animals were subjected to strenuous physical exertion so as to produce myocardial stress. Eight animals were subjected to the same physical stress but were not fed cholesterol.

3. Fifteen animals which had been fed cholesterol for 120 days were given single small doses of thrombin intravenously. Each of 8 animals which had not been fed cholesterol received a single small dose of thrombin intravenously.

4. To each of 10 healthy animals a single intravenous dose of Pituitrin alone was given, whereas an additional 21 healthy animals were given single doses of intravenous Pituitrin and thrombin in combination.

5. Animals which had been fed cholesterol for 2 months were given single doses of Pituitrin and thrombin separately and in combination.

Results

Cholesterol feeding alone. None of the animals which were fed diets high in cholesterol but which were not subjected to additional influences developed acute myocardial infarction (Table I). These animals developed marked atherosclerosis of the

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aorta and coronary vessel but in spite of narrowing of the lumens of the coronary arteries myocardial infarction did not occur Only small areas of fibrosis were found in the myocardium especially in the intramural branch of the left coronary artery (Figs 1 and 2)

Cholesterol feeding plus physical stress Twenty five cholesterol fed animals were subjected to intensive physical exercise in order to impose a stress on the myocardium The animals were made to run on a treadmill for 1 hour daily during the entire period of cholesterol feeding Serial electrocardiograms showed progressive signs of coronary failure In most of the animals episodes of cardiac asthma developed periodically and persisted to the end of the experiment Some of the animals died in the fourth and fifth months i e they did not survive the 6-month experimental period At necropsy large areas of myocardial necrosis (Fig 3) and scarring (Fig 4) secondary to arteriosclerotic changes were found in all of the animals. Inflammatory reaction in the perinecrotic areas a characteristic of myocardial in

Table I

Experimental conditions	Number of animals	*Number of animals with myocardial infarction (necrobiosis of heart muscle)*
1 Cholesterol feeding alone	22	0
2 Cholesterol feeding plus physical stress	25	25
Physical stress alone	8	0
3 Cholesterol feeding (120 days) and administration of thrombin	15	10
Administration of thrombin to healthy animals	8	0
4 Administration of Pitressin to healthy animals	10	[illegible]
Combined administration of Pitressin and thrombin to healthy animals	2	
5 [illegible]		



Fig 1 Cholesterol feeding only [illegible] that arteriosclerotic plaques almost completely [illegible] the lumens of the intramuscular branches of the left coronary artery (Sudan III)

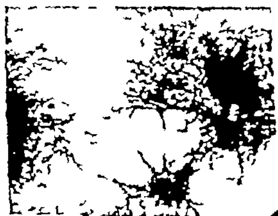
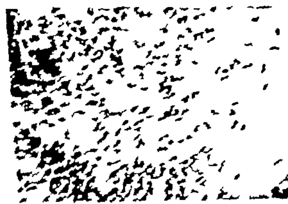


Fig 2 Cholesterol feeding only [illegible] the coronary [illegible] of the left [illegible]



[illegible]

farction was noted (Fig 3) In several rabbits aneurysm of the left ventricle had developed (Fig 5) Thrombosis was not found in any animal The areas of necrosis were distributed throughout the anterior lateral posterior and septal walls of the left ventricle and in the papillary muscles (See Fig 6)

In the control group of 8 animals subjected to the same physical stress but without cholesterol feeding moderate left ventricular hypertrophy was noticed at necropsy but no areas of necrosis were found in the myocardium in any of the animals (Table I)

COMMENT According to this data physical stress in the presence of coronary atherosclerosis is important in the pathogenesis of myocardial infarction



Fig 4 Cholesterol feeding plus physical stress Note the dense scar found in tissue removed from the posterior wall of the left ventricle (profocdum)



Fig 5 Cholesterol feeding plus physical stress The section was taken from the wall of an aneurysm of the left ventricle (profocdum)



Fig 6 Cholesterol feeding plus physical stress Coronal section of the entire heart of an animal with multiple myocardial infarct The black areas represent the sites of myocardial infarction

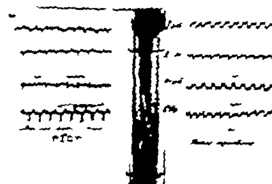


Fig 7 Cholesterol feeding plus administration of thrombin Electrocardiographic changes before and after the administration of a single dose of thrombin Note the depression of the S-T segment in Leads I II and CR₄ and the elevation of the S-T segment in Lead III after thrombin was given.

Cholesterol feeding plus administration of thrombin Cholesterol fed animals were administered a single small dose of thrombin intravenously The animals were given 3-4 c.c of thrombin (activity 12 seconds*) a dose which in 8 healthy animals did not produce coronary thrombosis (Fig 10 Table I) In the rabbits made arteriosclerotic by cholesterol feeding such small doses of thrombin led to formation of thrombosis and myocardial infarction in 10 of 15 animals (Figs 7 8 and 9)

COMMENT These experiments indicate that changes in the coagulability of blood play a definite role in the pathogenesis of myocardial infarction

*The activity of thrombin is determined according to the time which was necessary for clotting 0.1 ml. ... by 0.1 ml ... determined



Fig 8 Cholesterol feeding plus thrombin Note the thrombus obliterating one of the branches of the left descending coronary artery in the same animal whose electrocardiogram is shown in Fig 7 (Objective 20X ocular 7X)



Fig 9 Cholesterol feeding plus thrombin The myocardial necrosis and hypoxemia of the blood vessel occurred after the administration of 3 0 c c of thrombin intravenously (Objective 20X ocular 7X)

Combined administration of Pituitrin and thrombin to healthy animals In another group of animals the role of coronary spasm in the pathogenesis of myocardial infarction was studied Pituitrin (and in 8 experiments barium chlorid) was used to produce coronary arterial spasm The intravenous administration of 0 3 to 0 5 c c of Pituitrin did not produce any significant changes in the electrocardiograms of 10 healthy animals and at necropsy no areas of necrosis were found in these animals Additional experiments were carried out in which Pituitrin and thrombin were administered together to healthy animals This was done in order to investigate the possibility of producing acute coronary failure in the absence of coronary atherosclerosis under the influence of two factors namely spasm and altered coagulability of the blood The combined administration of Pituitrin and thrombin did result in electrocardiographic changes typical of an acute disturbance of the coronary circulation in 17 of 21 animals (Fig 10 Table I) At necropsy there were thrombi in the coronary vessels (Fig 11) myocardial ischemia and in animals which lived long enough (3 to 5 days) histologic changes such as are seen in myocardial infarction (Fig 12)

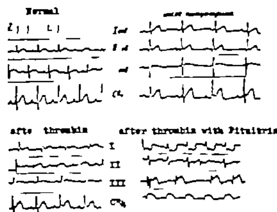


Fig 10 Combined administration of Pituitrin and thrombin to healthy animal Note that the administration of thrombin alone resulted in essentially no changes in the electrocardiogram whereas the administration of Pituitrin and thrombin in combination resulted in electrocardiographic changes consistent with acute posterior myocardial infarction



Fig 11 Combined administration of Pituitrin and thrombin to healthy animal Note the thrombus obliterating one of the branches of the left descending coronary artery The animal was given 4 0 of thrombin and 0.5 of Pituitrin intravenously (Objective 20X ocular 7 5X)

COMMENT. These results indicate that coronary arterial spasm in association with altered coagulability of the blood can lead to the formation of thrombus and myocardial infarction without organic involvement of the arterial wall by arteriosclerosis.

Administration of thrombin and/or Pituitrin to slightly arteriosclerotic animals. The administration of thrombin or Pituitrin alone to animals made slightly arteriosclerotic by short-term cholesterol feeding (2 months) did not result in myocardial infarction. However, the combined administration of thrombin and Pituitrin produced electrocardiographic and morphologic evidence of myocardial infarction (Fig. 13) and aneurysmal formation (Fig. 14, Table I).



Fig. 12. Combined administration of Pituitrin and thrombin to a healthy animal. Myocardial necrosis found at necropsy in an animal to whom 1.0 c.c. of thrombin and 0.5 c.c. of Pituitrin had been administered intravenously.



Fig. 13. Combined administration of Pituitrin and thrombin to a slightly arteriosclerotic animal. Longitudinal section of coronary blood vessels. The lumen of the vessel on the right is obliterated by a thrombus. The vessel on the left is patent. The animal was fed cholesterol for 35 days and received 3.0 c.c. of thrombin and 0.3 c.c. of *Pituitrin intravenously*.



Fig. 14. Combined administration of Pituitrin and thrombin to a slightly arteriosclerotic animal. Fresh specimen of the heart showing ventricular aneurysm.

Conclusions

1. A method for inducing myocardial infarction which more closely approximates the clinical conditions under which myocardial infarction develops in man has been described.

2. It has been shown that atherosclerosis of the coronary arteries is the most significant but not the sole factor in the pathogenesis of myocardial infarction.

3. The important role played by three additional factors in the development of myocardial infarction has been confirmed experimentally. These factors are (a) myocardial stress, (b) altered coagulability of blood, and (c) spasm of the coronary arteries.

Practical limitations of the Kety method for determining coronary blood flow by infrared analysis of blood nitrous oxide

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Fifteen years of experience on the part of one of us (J. H. H.) with the nitrous oxide method using both manometric and infrared analyses of blood gas has led us to the viewpoint expressed by Lord in an editorial earlier this year. This stressed the fact that the greatest need in the area of diagnostic studies in patients with coronary artery disease is the development of a precise test to measure coronary arterial blood flow in the human.[1] The lack of such a precise test seems to be an important limiting factor in the selection of patients for and hence the survival rate of those undergoing endarterectomy. Preliminary reports suggest that endarterectomy is one of the most promising surgical procedures for the alleviation of the disability of angina pectoris by increasing the flow of blood through the myocardium.

The complexity of the Kety–Van Slyke manometric method of analysis of nitrous oxide in the blood may have impeded its widespread utilization for determination of regional flows.[3] In particular, the approximate 5 per cent error in analysis as described by Gregg[4] has raised the question whether this indirect method of nitrous oxide analysis for coronary blood flow measurements is now the best approach. In 1953 Lawther and Bates[5] proposed a direct method of measuring nitrous oxide in blood using infrared absorption. A recent summary of applications of the nitrous oxide method for determining coronary blood flow in man was presented by Rowe, but no mention was made of the direct method of measuring nitrous oxide in blood by infrared analysis in this review. Bing[7] did not discuss the accuracy to be expected with the manometric nitrous oxide blood gas analytical procedure in his "Determination of Coronary Blood Flow," and did not refer to the direct method of measuring nitrous oxide in blood by infrared absorption.

Preliminary to attempting development of a simpler method of measuring coronary

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This investigation was supported in part by research grant (H[illegible]) from the National Heart Institute, [illegible] the Public Health Service, [illegible] part by grants [illegible] Committee (QH[illegible]) and the Committee on Problems of Al[illegible] the National Academy [illegible]—National Research Council (U[illegible]), C[illegible] Pharmaceutical Products, Inc., and the Heart Association of Southeastern Pennsylvania.

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blood flow applicable to both intact animals and man it was first necessary to have our team at Lankenau Hospital familiar with the limitations of the nitrous oxide manometric as well as the direct infrared analysis techniques It was expected that the new method using the radioactive isotope dilution principle could be quantitated by comparison with nitrous oxide measurements of coronary blood flow made simultaneously [4] This had been done when the indirect nitrous oxide method was calibrated against simultaneous direct measurement of coronary blood flow by means of a bubble flow meter [4]

The present progress report details the experience of the Lankenau group with the infrared absorption technique from 1953 through 1959 in making paired observations of coronary blood flow on anesthetized but otherwise intact dogs using the techniques of Eckenhoff and co workers [13] Particular attention is given to (1) a comparison of the precision of our measurement of the blood nitrous oxide concentration by means of the infrared absorption spectra of nitrous oxide with the precision acquired by analysts using the Van Slyke manometric technique and (2) a comparison of our experience with the results reported by Foltz using successive measurements of coronary blood flow in dogs under combination anesthesia

Methods

Our objective at Lankenau Hospital was to establish the reproducibility of an experimental design in which the same animals were tested repeatedly using the combined anesthesia morphine Dial urethane pentobarbital (MDUP) Since our preliminary report[1] in 1955 only minor changes have been made in the technique for measuring by infrared analysis blood nitrous oxide

Results

1 Measurement of nitrous oxide gas by infrared absorption The technique was reported by Lawther and Bates Before their paper was published arrangements were made with an American firm to make available a unit which has been in more or less continuous use in our laboratory Lawther and Bates had used an instrument manufactured in England

Our instrument has required some maintenance and tuning The constancy of the instrument was tested with calibrating mixtures Of interest in relation to the reproducibility of the physical instrument is our observation that an unknown gas containing approximately 740 parts per million (p p m) of nitrous oxide measured on eleven different days between April 1955 and July 1957 yielded readings varying between 723 and 756 p p m when compared with a standard gas containing 670 p p m of nitrous oxide

Measurement of nitrous oxide in blood The method used is essentially the same as that of Lawther and Bates However a dual extraction apparatu has been devised in order to save time in analyzing the pairs of arterial and coronary venous samples The procedure used to get the nitrous oxide out of the blood and to pass as a gas through the infrared analyzer follows the steps described by Lawther and Bates

The results with this method using human blood in which two different concentrations of nitrous oxide have been dissolved are shown in Table I Two concentrations were decided upon 2 36 ml per 100 ml of blood which would be a small amount for either a human cerebral or coronary blood flow and 7 65 ml which would be a large amount When our results are compared with those of Lawther and Bates (Table I) their analytical precision is not confirmed The two co workers in our laboratory have essentially the same degree of precision

3 Results of duplicate determinations of blood nitrous oxide gas when the nitrous oxide concentration is varied Since there are slight differences between human and dog blood we compared the per cent error of the analysts using the infrared technique *in dog blood only* with the results of the most experienced Van Slyke manometric analyst in our laboratory These observations are

*Details of th m thod hav been mimeographed and ar available by writing to th senior author This summary includes the steps involved in perf rming the animal studies from anesthesia to long-term care by our veterinarian

*Th instrument used i Model IR Nitrous Oxide Ana lyzed by he Li Becker D v of Beckman Instru ment I

Table I Infrared blood gas analyzer Reproducibility of method of measuring nitrous oxide content of blood

	Observers				
	Lawther and Bates 1953	La bens #1 1960		La bens # 1960	
		A	B	1	B
Mean of 20 determinations (ml N_2O per 100 ml blood)	4 36 ml /100 ml	2 36	7 65	2 38	7 55
Range	4 34–4 38	2 20 2 49	7 31 7 82	2 18 2 44	7 32 7 70
Standard deviation of individual differences	0 012	±0 07	±0 11	±0 07	±0 08
Coefficient of variation	±0 274%	3 0%	1 4%	2 9%	1 1%

recorded in Table II with the manometric analyses shown under *Observer #4*

This observer had errors which ranged from 18 to 2 per cent error was defined as the standard deviation in volume per cent divided by the average range in volume per cent the smallest standard deviation being ±0 09 volume per cent Kennedy [11] using human blood reports a standard deviation of ±0 009 volume per cent with the Kety modification and standard deviation of ±0 025 volume per cent with his micromethod

Three different observers used the infrared analysis method and all three had the same standard deviation (i e ±0 20 to 0 25 volume per cent) over the range tested This standard deviation compared favorably with the manometric technique in our laboratory the over all per cent error being 4 5 per cent for both methods The time saved through the use of the infrared method has been approximately 25 to 33 per cent

4 Errors involved in determining the arteriovenous differences of blood nitrous oxide concentrations in applying the desaturation method of measuring coronary blood flow The purpose of this analysis was to compare our data with those reported by Gregg[4] In the nitrous oxide procedure the technical error in determining the nitrous oxide arteriovenous difference can be judged from the fact that the average difference of duplicate nitrous oxide analyses for the 120 pairs was 0 030 volumes per cent the maximum difference being 0 065 volumes per cent Such differences can possibly introduce an error approximating 5 per cent since the mean nitrous oxide arteriovenous difference during a test run varied in different experiments from 0 35 to 1 5 volumes per cent with an average difference of 0 8 volumes per cent

In order to analyze our data for comparison in the same flow range as Gregg i e 40 to 150 c c we graphed the twenty one coronary blood flow curves determined by infrared arteriovenous nitrous oxide differences within the range of 40 to 150 c c /100 Gm /minute and twelve resulting from a Van Slyke manometric analysis of blood gas All data were derived from observations of coronary blood flow made in the dogs under morphine Dial urethane pentobarbital anesthesia (MDUP) in control studies

The average arterial nitrous oxide (N_2O) concentrations for 1 2 4 6 8 and 10 minutes of the desaturation curves were plotted along with the same points on the coronary venous curves giving average arteriovenous values These values are shown in Table III

The standard deviation given is that of the infrared analysis or manometric technique in the various ranges of blood N_2O in cubic centimeters per 100 c c blood The per cent error is the standard deviation divided by the average arteriovenous value This table shows that the percentage error tends to increase reaching the greatest level at the tenth minute Since the coronary blood flow value is heavily weighted by the denominator which is the integrated arteriovenous difference the precision of the analytical method is practical importance

Table II Results of duplicate determinations of dog blood with varying concentrations of nitrous oxide

	Observer #1			Observer #2			Observer #3			Observer #4†		
Range (ml / 100 ml blood)	Number of duplicate observations	S D	Per cent error*	Number of duplicate observations	S D	Per cent error	Number of duplicate observations	S D	Per cent error	Number of duplicate observations	S D	Per cent error
0–1	3	0 12	24	4	0 06	12	2	—	—	7	0 09	18
1 2	27	0 20	13	15	0 25	17	10	0 0>	3	26	0 23	15
2–3	28	0 22	9	11	0 23	9	12	0 10	4	17	0 38	15
3–4	7	0 31	9	5	0 28	8	5	0 12	3	12	0 22	6
4–5	12	0 09	2	7	0 15	3	3	0 30	6	33	0 14	3
5–6	13	0 37	7	37	0 31	6	1	—	—	45	0 13	2
6–7	53	0 27	4	52	0 23	4	16	0 27	4	6	0 20	3
7 8	59	0 23	3	15	0 19	3	57	0 17	2	1	—	—
8–9	1	—	—	—	—	—	1	—	—	—	—	—
9–10	—	—	—	—	—	—	1	—	—	—	—	—
Total range 0–10	203	0 25	5	146	0 23	5	108	0 20	4	147	0 20	4

*Per cent error = Standard deviation in volumes per cent / Average range volumes per cent

†These determinations were made using [illegible] modification of the Orcutt Waters method using the Van Slyke manometric apparatus

5 *Measurements of coronary blood flow in anesthetized dogs*

A FIRST STUDIES COMPLETED IN 53 DIFFERENT EXPERIMENTS ON 14 DOGS Foltz and co workers[19] in 1950 had reported that depending upon the anesthesia used (pentobarbital or MDUP) quite different levels of cardiac activity were obtained *Both* anesthetic agents show rather wide standard deviations for the population which we have interpreted as indicative of rather wide biological variation between animals but which also represent undoubtedly a considerable variation in response to anesthesia

Because repeat measurements of coronary blood flow in human beings at later times are unlikely and because our application of the method permitted recovery of an animal after the study we decided to extend the Foltz investigation by making successive observations on a lesser number of dogs The purpose was to determine how reproducible our measurements of the levels of coronary flow might be using infrared analysis of blood nitrous oxide with simultaneous measurements of cardiac oxygen metabolism cardiac rate and work

The results are summarized in Table IV Under the combination anesthesia (MDUP)* the mean flow values were 91 c c standard deviation ±33 and coefficient of variation ±36 per cent The flow values measured under the combination anesthesia are essentially the same as reported by Foltz and associates[9] (Table III) We observed slightly higher levels of coronary flow cardiac arteriovenous oxygen extraction and cardiac work When MDUP anesthesia was used the mean cardiac rate was 74 with a standard deviation of ±25 and when pentobarbital was used it was 162 with a standard deviation

*Th[illegible] technique [illegible] as follows The total dose of morphine 3 0 mg per kilogram T[illegible] th[illegible] of the initial dose is given subcutaneously 45 minutes before the intrav[illegible] injection This consists of equal parts by volume of pentobarbital (65 mg./c.c.) and the Dial urethane mixture the total being 0.30 c.c per kilogram I[illegible] 0 15 c.c of pentobarbital and 0 15 c.c of Dial urethane This is supplied by Ciba Pharmaceutical Products Inc. About 1 to 1½ hours after the first morphine dose the animal having been operated upon and the catheters placed properly 1/4 of the total dose is given intramuscularly 30 minutes before the [illegible] of saline for the first measurement of coronary blood flow and cardiac output Just after th[illegible] study is completed and approximately 30 minutes before observation #2 [illegible] comparable dose of morphine is given again intramuscularly This is usually 30 minutes before any drug stimulus is introduced

of ±19 The most striking difference was a standard deviation in coronary flow values three times that reported by Foltz in his pentobarbital series This shows that in a group of 6 dogs with 28 different observations as compared to Foltz observations (19) in 19 dogs we have observed similarly rather wide biological variation Thus we have confirmed Foltz observations by means of another method of quantitating the nitrous oxide in blood that coronary blood flow and cardiac oxygen uptake are greater under pentobarbital anesthesia the heart rate being more than twice as rapid

B COMPARISON OF MEAN VALUES FOR 37 CORONARY BLOOD FLOW OBSERVATIONS IN SAME DOGS AFTER SHORT AND LONG INTERVAL This analysis was made in an attempt to discover whether the variation in coronary blood flow and cardiac oxygen consumption was due to wide biological variation between animals [10] or to some factor inherent in the lability of coronary blood flow These observations were carried out in fewer dogs All observations made under the same anesthesia when a drug was not being studied were compared The data are presented in Table V and show the mean values of the first run compared with the mean values of the second run in the 8 dogs (37 comparisons) under the combination anesthesia Under this (MDUP) anesthesia the variation in coronary blood flow at four week intervals was essentially the same as that recorded when the observations were repeated after 30 to 40 minutes

Discussion

We conclude that in our laboratory the infrared analytical technique is not so precise as that reported by Lawther and Bates, and does not approach the rigorous requirements for manometric analysis set up by Kety[3] and met by Gregg[4] However this method does save 25 to 33 per cent of time as compared with the manometric technique and the per cent error is about the same as that of the most experienced Van Slyke analyst in our laboratory The percentage figure above for reduced analytical time included the time required for another blood gas analysis if a single one of the five paired nitrous oxide blood concentrations did not fall on a smooth curve drawn for the flow thus requiring a recheck [8]

The most obvious factor other than biological variation which might be causally related to the large percentage coefficient of variation in coronary blood flow measurements using nitrous oxide is the blood gas analytical method Our results are interpreted as indicating that the infrared analytical method must be further improved in order to reduce the technical error recorded here in determining the nitrous oxide arteriovenous oxygen difference It would seem that this is a twofold problem requiring greater skill on the part

Table III Average arteriovenous differences of nitrous oxide during 10 minute period of desaturation

Morphine Dial urethane pentobarbital anesthesia

	Van Slyke manometric analysis			*Infrared analysis*		
	12 Coronary flows (40 150 /100 Gm /min)			*21 Coronary flows (40 150 c.c./100 Gm /min)*		
	Average A V	*S D*	*Per cent error**	*Average A V*	*S D*	*Per cent error*
First min	1 70	0 20	11 8	1 6	0 [illegible]	3[illegible]
Second min	1 54	0 24	15 6	1 39	[illegible]	1[illegible] 5
F[illegible]rth min	0 80	0 28	35 0	0 90	[illegible]	22 2
Sixth min	0 3[illegible]	0 21	33 9	0 50	[illegible]	3[illegible] 0
Eighth min	0 24	0 21	87 6	0 29	[illegible]	[illegible] 6
Tenth m[illegible]	0 14	0 09	64 3	0 11	[illegible]	[illegible]

Average A V c.c.N₂O/100 c. blood
Standard deviation [illegible] of the [illegible] analysis [illegible] of blood [illegible] level
*Per cent error S D divided by average A V

Table IX. First studies completed in 53 different experiments on 14 dogs weighing from 26 to 48 kilograms

Coronary blood flow (100 Gm./min.)

	Mean	S.D.	Per cent coefficient of variation
Pentobarbital anesthesia*	17	73	4[illegible]
Morphine-Dial-urethane pentobarbital anesthesia†	91	33	36

*8 different experiments on 6 dogs.
†45 different experiments on 8 dogs.
S.D. Standard deviation of the individual differences from the mean difference.
Per cent coefficient of variance. The ratio of the standard deviation of the individual difference to the actual mean value of the parameter.

Table X. Comparison of mean values for 37 coronary blood flow observations in same dogs after short and long interval

Coronary blood flow (c.c./100 Gm./min.)

	Observation period 1	Observation period 2	S.D. differences	Per cent coefficient of variation
Morphine-Dial-urethane (30-40 min.)	94	90	25	26
Pentobarbital anesthesia (4 weeks)	86	76	27	31

S.D. difference. Standard deviation of the individual differences from the mean difference.
Per cent coefficient of variation. The ratio of the standard deviation of the individual difference to the actual mean value of the parameter.

of the analyst and better instrumentation so that the results reported by Lawther and Bates (Table I) might be approached in this hemisphere.

Even though analytical precision is improved, spurious and erroneous results may develop when the nitrous oxide method is used for measuring regional blood flow in biological systems, as pointed out by Sapirstein.[17] With infrared analysis no experiments had to be discarded either because of failure to obtain smooth curves or because the final arteriovenous nitrous oxide difference was greater than 0.3 volume per cent, the level above which most workers agree that discard is indicated. During the period covered in this report only three flows involving the manometric technique of nitrous oxide analysis were discarded.

From this survey of the precision of our analytical methods and from the negative results obtained from the application of the radioisotope-dilution technique developed in this laboratory, it is evident that there is still need for devising a simpler method of measuring coronary blood flow in animals, and Bing and associates[18] have recently reached the same conclusion with reference to human beings.

Summary

This report provides data bearing on inconstancies and perhaps inaccuracies which are present when the nitrous oxide method is applied in the measurement of regional blood flow, such as coronary blood flow.

The manometric technique used for eight years in a study of both cerebral and coronary blood flow was replaced by infrared nitrous oxide blood gas analysis during the past seven years. The limitations of this method are categorized under these headings: (1) measurement of nitrous oxide gas by infrared absorption, (2) measurement of nitrous oxide gas in blood, (3) results of duplicate determinations of blood nitrous oxide gas at a low and a high blood nitrous oxide concentration, (4) errors involved in determining the arteriovenous differences of blood nitrous oxide concentrations, and (5) applications of the Kety nitrous oxide desaturation method to measurements of coronary blood flow in anesthetized intact dogs on successive occasions.

We conclude (1) that the blood analytical technique using the principle of infrared absorption is practical, time saving, and comparable in precision to the manometric method and (2) that during steady states the Kety nitrous oxide test is quantitative and reproducible and at the present time is the best method of measurement of coronary blood flow in intact animals.

REFERENCES

1. Lord, J. W., Jr.: Surgery for coronary artery disease, Surg. Gynec. & Obst. 110:746, 1960.
   Longmire, W. P., Jr., Cannon, J. A., and Kattus, A. A.: The surgical treatment of angina pectoris, A. M. A. Arch. Int. Med. 101:886, 1959.
3. Kety, S. S.: The quantitative determination of cerebral blood flow in man, Methods in Medical

Research Vol 1 Chicago 1948 Year Book Publishers Inc p 204
4 Gregg D E Longino F H Green P A and Czerwonk L J A comparison of coronary flow determined by the nitrous oxide method and by a direct method using the rotameter Circulation 8 89 1951
5 Lawther P J and Bates D V A method for determination of nitrous oxide in blood Clin Sc 12 91 1953
6 Ross G G The nitrous oxide method for determining coronary blood flow in man Am HEART J 58 768 1959
7 Bing R J Determination of coronary blood flow Methods Medical Research Vol 8 Chicago 1960 Year Book Publishers Inc p 269
8 Forte I Williams A J Schmitthenner J F Neal H Woske H Richards R and Hafkenschiel J H Coronary blood flow using radioact iodine compared with nitrous oxide Fed Proc 19 90 1960
9 Eckenhoff J E Hafkenschiel J H Harmel M H Goodale W T Lubin M Bing R J and Kety S S Mea urement of coronary blood flow by the nitrous oxide method Am J Physiol 152 356 1948
10 Foltz E L Page R G Sheldon W F Wong S K Tuddenham W J and Weiss A J Factors in ariation and regulation of coronary blood flow in intact anesthetized dogs Am J Phy iol 162 521 1950
11 Goodale W T and Hackel D B Mea ure ment of coronary blood flow in dogs and man from rate of myocardial nitrous oxide desatura tion Circulation Res 1 50 1953
12 Forte I Williams A J Potgieter L Schmitt henner J E Hafkenschiel J H and Riegel C Coronary blood flow and cardiac oxygen metabolism during nicotine induced increases in left entricular work Ann New York Acad Sc 90 174 1960
13 Forte I E Potgieter L and Schmitthenner J E Effects of hypertension on arterial pressure heart work and cardiac oxygen utilization Circulation P 8 1218 1960
14 Hafkenschiel J H Determination of cerebral blood flow in man using an infrared nalyzer to measure blood nitrous oxide Fed Proc 14 67 1955
15 Kennedy C A micromethod for determination of nitrous oxide in blood J Appl Phy iol 11 141 1957
16 Mainland D The treatment of clinical and laboratory data Edinburgh 1938 Oliver and Boyd
17 Sapirstein L A nd Ogden E Theoretic limitations of the nitrous oxide method for the determination of regional blood flow Circula tion Res 4 245 1956
18 Bing R J Hellems H K nd Regan T J Mea urement of coronary blood flow in man Circulation 22 1 1960

Hemodynamic responses to administration of mephentermine in normotensive and hypotensive dogs

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Mephentermine sulfate† is used effectively in the treatment of hypotension.[1-3] There is confusion, however, concerning the mechanism by which the drug restores arterial pressure. In acute hypotension secondary to section of the spinal cord, sympathectomy, ganglionic blockade, and in the use of certain anesthetic agents, there may be loss of venomotor tone and pooling of blood in the periphery of the body.[4] This reduces venous return and leads to a fall in cardiac output. The decreased cardiac output rather than a loss of arteriolar tone appears to be the major cause of the hypotension.[5] It might be desirable to restore perfusion pressure in such cases by using a vasopressor drug which increases venous tone and cardiac output, rather than one which produces severe arteriolar constriction. Mephentermine is of interest because it has been reported by some to have little effect on peripheral resistance.

Brofman and co-workers[7] found no change in cardiac output in dogs or man after the administration of mephentermine even though arterial pressure increased. They attributed the increased pressure to increased peripheral resistance. Others[8] report that the drug has little effect on peripheral resistance but that it increases the force of myocardial contraction. Because of these conflicting ideas, we re-examined the hemodynamic effects of mephentermine in dogs.

Methods

The experiments were done on intact mongrel dogs. The 6 animals in Group I were anesthetized lightly with thiopental sodium, treated with gallamine triethiodide,‡ intubated, and ventilated with a fixed volume respirator. End-expiratory concentration of carbon dioxide was monitored continuously with a Liston Becker carbon dioxide analyzer. Ventilation was adjusted initially so that end-expiratory concentration of carbon dioxide was about 4 per cent. Repeated doses of gallamine were given at 30-minute intervals in order to maintain relaxation of skeletal muscle. The dogs of Group II were prepared in the same way

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†Wyamine, Wyeth Laboratories, Philadelphia, Pa.

‡Flaxedil, Lederle Laboratories, American Cyanamid Co., Pearl River, N.Y.

but in addition they were made hypotensive with intravenous injections of 100 mg of hexamethonium. Three dogs in Group I were included in this group. They were made hypotensive after a 30 minute recovery period which followed the administration of mephentermine. The other 3 dogs were prepared as described and ganglionic blockade was induced without prior administration of mephentermine. The dogs of Group III were anesthetized with intravenous pentobarbital sodium, 30 mg per kilogram. These animals were not ventilated artificially. No effort was made to control their end expiratory CO_2 tension or arterial oxygen saturation. The dogs of Group IV were the same animals used in Group III. Hexamethonium was administered to these after a 30 minute recovery period.

Two catheters were inserted through an external jugular vein. The tips were placed at the junction of the superior vena cava and right atrium. Needles were placed in the left carotid and femoral arteries and in the femoral vein. Cardiac output was measured by the indicator dilution method with injections of indocyanine green dye into the right atrium. Dyed blood was drawn from a carotid artery through a Gilford densitometer and time concentration curves were recorded with a Sanborn direct writing oscillograph. The blood was returned to the animal after each withdrawal by reversing the motor on the pump. Loss of blood was negligible except for the 50 ml taken at the beginning of the experiment to calibrate the densitometer. Femoral arterial and right atrial pressures were recorded continuously by means of Statham strain gauges.

About one hour was required to set up the experiment after the animal was anesthetized. This was ample time for disappearance of the effects of thiopental in the animals of Groups I and II. Several dye curves were obtained during the next 15 to 30 minutes in order to establish control values. Mephentermine sulfate, 0.3 to 0.6 mg per kilogram in 3 to 5 ml of normal saline, was then injected into the femoral vein. Dye curves were obtained when arterial pressure became stable after having reached its maximal level. Curves were obtained in some animals at irregular intervals for 30 minutes after the injection of mephentermine.

Cardiac output was calculated according to the method of Hamilton.[8] Mean blood pressures were obtained by electrical integration of the output of the strain gauges. Peripheral resistance was determined by dividing the difference between mean arterial and right atrial pressures by cardiac output. The results are expressed in arbitrary units. Heart rate was determined by counting arterial pulses at the time of inscription of the dye curves. The data were analyzed according to methods described by Fisher.[9]

Results

The data from 22 experiments performed on 14 dogs are summarized in Table I. The data are grouped according to the control state of the animals. The responses to mephentermine in the different groups cannot be compared quantitatively, however, because of the differences in the dose of the drug.

An increase in arterial pressure was noted in each dog after rapid intravenous injection of the mephentermine. The increase appeared within 1 minute after the injection, and the peak response occurred in 2 to 4 minutes. The return of the pressure to control levels took place gradually over a period of 20 to 30 minutes. There was a tendency for mean right atrial pressure to increase in each group, but the changes were small and not considered to be significant.

Cardiac output increased in each of the 22 experiments regardless of the control state of the animal before the administration of mephentermine. In 8 dogs the cardiac output was measured 1 minute after the injection. It was found to be unchanged in 5 of them even though arterial pressure had increased appreciably in all 8. This observation suggests that the drug causes an increase in arteriolar tone before the heart increases its output. The increased output appeared soon after the initial increase in arteriolar tone and persisted for about 30 minutes. The stroke volume increased in 20 of the 22 experiments. The relatively low control values in Groups I and II may be attributed to the tachycardia secondary to the selective vagolytic action of the gallamine. Changes in heart rate were

Table I Hemodynamic responses to the administration of mephentermine

Dog number	Dog eight (kg)	Dose (mg/kg)	Mean arterial pressure (mm Hg)		Mean right atrial pressure (mm Hg)		Cardiac output (ml/min)		Stroke olume (ml)		Heart rate (beats/min)		Peripheral resistance (units)	
			Bef re	After	Before	After	Before	After	Before	After	Before	After	Before	After
Group I														
1	15 3	0 49	140	230	8 5	8 8	1 794	2 328	9 3	12 9	192	180	78 0	98 8
2	14 5	0 52	130	160	7 5	8 2	2 856	3 168	16 6	22 0	186	144	43 5	50 5
3	19 1	0 39	127	185	4 8	5 0	1 452	1 800	6 7	13 0	216	138	87 5	102 8
4	10 5	0 34	130	175	5 4	4 7	1 890	2 166	9 3	8 9	228	246	68 8	80 8
5	18 7	0 40	117	240	9 5	10 7	3 768	4 48	16 1	20 0	234	220	31 1	53 5
6	20 5	0 30	130	175	7 2	8 2	2 766	3 444	15 4	22 0	180	156	47 0	50 8
Mean	16 4	0 41	129	194	7 2	7 6	2 421	2 898	12 1	16 5	206	181	59 7	72 9
Standard error of mean difference			14 2		0 23		78 0		0 92		13 2		3 19	
Probability			< 0 01		< 0 2		< 0 01		< 0 01		< 0 2		< 0 01	
Group II														
2	14 5	0 52	105	135	7 5	7 5	1 908	2 736	9 9	13 0	192	210	55 0	49 3
4	10 5	0 34	100	178	5 0	4 8	1 380	1 854	6 2	7 9	222	234	72 5	96 0
5	18 7	0 40	122	230	8 5	8 8	256	3 246	10 2	12 9	222	252	54 1	70 9
7	15 5	0 48	125	240	5 0	5 0	1 160	1 254	6 4	5 3	180	234	107 8	191 4
9	16 5	0 45	60	250	4 7	7 6	954	1 554	6 9	9 6	138	162	62 9	160 9
9	26 5	0 28	120	310	2 0	2 6	3 138	4 146	19 4	19 2	162	216	38 2	74 8
Mean	17 0	0 41	105	224	5 5	6 1	1 799	2 465	9 8	11 3	186	218	65 1	107 2
Standard error of mean difference			25 7		0 47		143 0		0 71		7 4		16 46	
Probability			< 0 01		< 0 3		< 0 01		< 0 1		< 0 01		< 0 05	

Group III														
10	16 4	0 46	148	200	3 0	5 7	2 604	3 252	16 7	18 7	156	174	56 8	61 5
11	21 5	0 0	133	150	5 0	6 0	2 02	2 778	14 0	20 1	150	138	65 8	54 0
12	19 3	0 30	140	170	8 0	7 8	2 094	2 742	15 9	21 8	132	126	66 9	62 0
13	22 5	0 30	100	150	8 0	7 0	2 582	4 872	33 2	36 9	104	132	38 7	30 8
14	17 5	0 10	100	143	5 7	5 5	034	2 34	14 7	15 8	138	174	49 3	51 9
Mean	19 4	0 33	124	161	6 3	6 4	2 467	3 280	18 9	22 7	137	149	55 5	52 0
Standard error of mean difference			6 6		0 36		121 0		1 0		9 1		2 8	
Probability			< 0 01		< 0 3		< 0 01		< 0 02		< 0 3		< 0 4	
Group IV														
10	16 4	0 30	105	150	4 6	4 9	1 998	238	10 1	11 3	198	214	52 6	67 0
11	21 5	0 30	120	200	6 3	6 0	2 442	3 298	13 6	16 3	190	108	49 1	60 8
12	19 3	0 30	125	200	5 5	6 0	2 730	3 174	15 2	24 5	180	102	45 8	63 0
13	22 5	0 30	88	137	4 7	3 9	4 092	5 250	27 3	8 2	150	186	21 5	26 1
14	17 5	0 30	103	165	5 0	6 7	2 508	3 018	15 2	16 2	165	186	41 9	54 7
Mean	19 4	0 30	109	170	5 3	5 5	2 754	3 394	16 3	21 3	175	163	42 2	54 3
Standard error of mean difference			6 9		0 44		162 0		2 5		26 1		2 10	
Probability			< 0 001		< 0 7		< 0 02		< 0 2		< 0 7		< 0 01	

Group I Treated with pentobarbital sodium No ganglionic blockade
Group II Treated with pentobarbital sodium Ganglionic blockade with hexamethonium
Group III Anesthetized with pentobarbital sodium No ganglionic blockade
Group IV Anesthetized with pentobarbital sodium Ganglionic blockade with hexamethonium

variable and not significant in most groups

Calculated peripheral resistance increased in 18 of the 22 experiments

Discussion

Mephentermine has been reported to increase the force of myocardial contraction[6-11] Recent evidence indicates that this is an indirect effect produced by the release of catecholamines[11] We found that the drug causes peripheral venous constriction and a shift of blood from the peripheral vessels in man[13] If it causes blood to be pushed centrally and if it also increases the force of myocardial contraction it might be expected to increase cardiac output An increased output was observed regularly in these experiments

The increase in peripheral resistance seen in most of the dogs indicates that mephentermine caused a decrease in the caliber of the arterioles A decrease in caliber in the face of an increase in arteriolar distending pressure and blood flow could be caused only by an increase in arteriolar tone We ... evaluate the degree of increased ...iolar tone from these studies but Borden and Haddy[14] found that mephentermine caused less arteriolar constriction in the forelimb of dogs than did norepinephrine or metaraminol Regardless of the magnitude of the arteriolar response it appears that mephentermine may elevate arterial pressure by increasing both cardiac output and peripheral resistance

Summary

The hemodynamic responses to mephentermine were studied in dogs anesthetized with pentobarbital and in those treated with gallamine Observations were made in normotensive animals and in animals made hypotensive by intravenous hexamethonium

Mephentermine regularly caused an increase in cardiac output and arterial pressure regardless of the control state of the animal Calculated peripheral resistance increased in 18 of the 22 experiments

In this study mephentermine raised the level of arterial pressure by increasing both cardiac output and peripheral resistance

REFERENCES

1 Hellerstein H K Brofman B L and Caskey W H Shock accompanying myocardial infarction treatment with pressor amines Am Heart J 44:407 1952
2 Blundell A E Pillon J W and Ambro F P Mephentermine—a clinically useful and effective pressor amine Anesth & Analg 35:483 1956
3 Brofman B L Hellerstein H K and Caskey W H Mephentermine—an effective pressor amine Am Heart J 44:396 1952
4 Weil M H Current concepts on the management of shock Circulation 16 1097 1957
5 Smith J R and Hoobler S W Acute and chronic cardiovascular effects of pentolinium in hypertensive patients Circulation 14:1061 1956
6 Welch G H Braunwald E Case R B and Sarnoff S J The effect of mephentermine sulfate on myocardial oxygen consumption myocardial efficiency and peripheral vascular resistance Am J Med 24:871 1958
7 Aviado D M Jr Cardiovascular effects of some commonly used pressor amines Anesthesiology 20 71 1959
8 Hamilton W F Moore J W Kinsman J M and Spurling R G Studies on the circulation IV Further analysis of the injection method and of changes in hemodynamics under physiological conditions Am J Physiol 99:534 1932
9 Fisher R A Statistical methods for research workers ed 10 Edinburgh 1946 Oliver and Boyd Ltd
10 Cares P C Goldberg L I and Darby T D Heart force effects of sympathomimetic amines as a basis for their use in shock accompanying myocardial infarction Circulation 8 883 1953
11 Goldberg L I Cotten M Darby T D and Howell E V Comparative heart contractile force effects of equipressor doses of several sympathomimetic amines J Pharmacol & Exper Therap 108 177 1953
12 Swaine C R Perlmutter J and Ellis S Mechanism of action of mephentermine Fed Proc 19 122 1960
13 Horsley A W and Eckstein J W The effect of mephentermine on peripheral venous tone Clin Res 7:238 1959
14 Borden C and Haddy F J A comparison of the peripheral vascular effects of certain sympathomimetic amines Clin Res 7:237 1959

Salvage of heart muscle by fibrinolytic therapy after experimental coronary occlusion

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Fibrinolytic therapy has been used for the lysis of large thrombi of arterial or venous origin in many experimental and clinical situations, including myocardial infarction in man. This type of therapy of coronary occlusion and myocardial infarction seems logical, but two serious theoretical objections must be considered. First, even under ideal circumstances an average of 3 to 6 hours is necessary for the lysis of thrombi, a period considered to be too long to protect against the tissue breakdown which is said to be inevitable after myocardial ischemia of only 30 to 45 minutes' duration. Second, in at least 40 per cent of the patients who die of coronary thrombosis and myocardial infarction, fresh coronary thrombi cannot be demonstrated at autopsy, and there would thus be no obvious therapeutic target for clot dissolving agents.

The evidence for such short-lived myocardial viability is based upon many studies in which no attempts had been made to alter either the coagulability of the myocardial blood supply or the metabolic state of the myocardium during this period of deprivation. Necrosis appeared to be inevitable after ischemia in excess of 30 minutes in these studies.

The myocardium may resist anoxia for more than 2 hours without irreversible effects on its function when the coronary system is perfused with heparin or during hypothermia. Myocardial excitability, energy production, and energy utilization deteriorate at different rates during anoxia, indicating gradations of resistance of biochemical and biophysical processes of the heart to ischemia.[3] An isolated myocardial fiber can continue to utilize nutriment, contract and relax, and perform work after 6 months in proper nutrient media. These are but a few of the factors that must be studied before we can define the final limits of myocardial viability. The heart may actually function under conditions previously considered inimical to its integrity.

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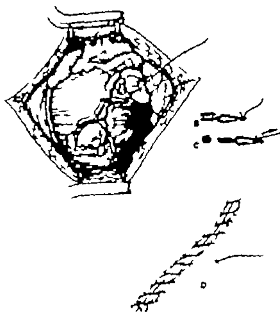


Fig 1 Technique of temporary coronary artery occlusion

In our previous experiments we noted a profound alteration in the early micropathology of the heart after fibrinolytic treatment of experimental coronary thrombi[1] The large thrombi in the major coronary artery were consistently lysed At the same time minute fibrin thrombi in the microcirculation (arterioles capillaries and venules) and interstitial collections of edematous fluid which apparently was rich in protein were noted in the control dog hearts but were absent in the fibrinolytic treated animal Deposition of epicardial fibrin and vascular congestion were also significantly reduced in fibrinolytic treated dogs We postulated that this microblockade during initial phases of infarction might contribute to the irreversible damage of these marginal zones and that the fibrinolytic dissolution of this blockade could salvage these areas We felt that it was necessary to determine whether this fibrinolytic treatment could extend the viability of the myocardium for prolonged periods of time

The present series of experiments was designed to study whether fibrinolytic enzymes could exert an important effect upon myocardial viability apart from their gross clot dissolving action as suggested by our previous study Infarcts were produced as uniformly as possible by occluding the left anterior coronary artery immediately distal to its first side branch for a standard period of time and assessing the end result of enzyme treatment by comparing the size and structure of infarcts in a treated and a control group Extension of viability would thus be reflected in a reduction in the size of infarcts whereas deleterious effects should be manifested by larger areas of necrosis The structural alterations were analyzed in finer detail by microscopic study

Methods

Mongrel dogs were anesthetized with intravenous sodium pentobarbital and intubated Artificial respiration was maintained with ambient air through a Harvard respirator Under aseptic technique the thorax was entered through the fourth left intercostal space The left anterior descending coronary artery was dissected and then occluded by a vascular clamp immediately below its first side branch (The anatomy of this region was remarkably constant allowing consistent levels of ligation) Braided No O silk or monofilament nylon string was tied to the clamp and led through a distant intercostal space through the chest wall The chest was then closed After 3 hours the string was firmly pulled taut removing the occluding clamp from the artery (Fig 1)

The animals were divided into control and treated groups at random In the treated group a continuous infusion of fibrinolysin* was initiated 2 hours after coronary artery occlusion and continued for a total of 5 hours (1 hour before and 4 hours after removal of the clamp) In all animals specimens of blood were tested for fibrinolytic activity by the euglobulin method[8] before operation at the time of removal of the clamp during and at the termination of the infusion and then daily until autopsy

The dogs were autopsied at intervals up to 21 days Before autopsy they were hepar

*Mixture of crude human plasminogen (Merck Sharp & Dohme Lot N 1108 M?) 10 000 Christensen units per hour after activation by streptokinase and [illegible] crude human plasminogen (Ortho) 60 000 units per hour after activation with Varidase (Lederle—streptokinase and [illegible]) 2 900 units per hour [illegible] mixture [illegible] varying fibrinolytic and [illegible] activity due to the [illegible] human plasma and [illegible] of [illegible] degree

tized and sacrificed by the injection of 20 to 50 c c of sodium pentobarbital intravenously. The hearts were removed gently so as not to dislodge any thrombi and the position of the vascular clamp was identified within the chest. The coronary arteries were then carefully dissected and opened to verify their patency. The hearts were finally transected serially from base to apex at intervals of 1 cm starting immediately below the site of previous coronary artery occlusion. The areas of infarction were identified in the gross fresh specimens and measured in each transection of the specimen as accurately as possible. Histologic sections were obtained from the central and marginal zones of the infarcted area and the presumably normal posterior wall of the left ventricle at the same level of transection (Fig 2). One of us (C B) analyzed all histologic sections in detail without knowledge of whether the animal had received treatment.

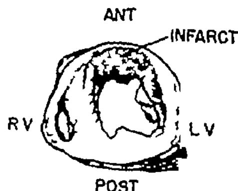


Fig 2 Transverse section of entire heart illustrating region of infarction

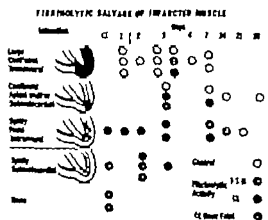


Fig 3 Gross extent of myocardial infarction. Open circles = control; solid circles = treated animals, euglobulin lysis times shorter than 1 hour; shaded circles = treated animals, euglobulin lysis times 1 to 2 hours; and solid circles with crosses = treated animals hemorrhagic death. Note the preponderance in the control animals of infarction in the large confluent transmural group contrasted with the infarcts in more distal and subendocardial regions in the treated animals.

Results

Fifty two animals were operated upon. Ten were eliminated because they died acutely within 1½ hour after occlusion with the clamp still in place and thus could not be regarded either as control or treated animals. Evaluation of the experimental data demonstrated that the therapeutic effect was closely related to the circulating fibrinolytic activity. The degree of fibrinolytic activity in the treated group of 26 animals showed a marked variation despite constancy of dosage and duration of plasmin treatment. The fibrinolytic activity (lysis time of a standard fibrin clot) was less than 1 hour in 15, 1 to 2 hours in 5 and more than 2 hours in 6 animals. All 16 control animals showed lysis times of more than 5 hours, i e little evidence of spontaneous lysis. Infarcts equal in size to those of the control animals were seen in all of the 6 animals in which the lysis times were longer than 2 hours.

This variability of response of the euglobulin lysis time to the standard dose of fibrinolysin was expected since no consideration was made of variations in the weights of the dogs, the levels of circulating inhibitor, etc. In subsequent experiments we are now employing a modification an in vitro dose prediction method [23] and are able to accurately produce consistent levels of circulating fibrinolytic activity.

Gross extent of infarction Fig 3 demonstrates the diminution in extent of myocardial infarction after fibrinolytic therapy. A significant alteration in location of the infarcts is seen, the areas of infarction in the treated animals tending to be spotty, located in the more distal apical portions and subendocardial rather than large confluent and transmural. Eleven of 16 control animals showed extensive confluent transmural infarcts. Somewhat smaller infarcts in 4 of the other animals were in



Fig 4A Large confluent transmural infarction (control)

infarcts that were 7 days old or older a length of time in which shrinkage from the contraction of fibrous replacement tissue would be expected

Those animals in which the lysis times were 1 hour or less had the smallest infarcts The extent of infarction in animals in which the lysis times were between 1 and 2 hours was intermediate between that in the control and that in the adequately treated groups

Six treated animals died from extensive hemorrhage into the chest (black circles with white crosses in Fig 3) 3 within 12 to 24 hours 2 within 48 hours and 1 in 72 hours The 3 animals which died within 12 hours do not constitute a valid group for determining gross extent of infarction since such early infarction does not lend itself to accurate measurement These treated animals died from an oozing into the chest cavity from the surgical wound as a result of the treatment

This increased mortality was not unexpected in the treated group despite meticulous attempts at hemostasis but was not due to infarction per se and fortunately would find no analogy in a clinical situation Many animals were rendered afibrinogenemic as a result of the intense induced fibrinolysis and proteolysis

Fig 4A shows a typical large confluent transmural infarct in a control animal 3 days old and this is in contrast to a small spotty subendocardial infarct in a treated animal shown in Fig 4B At the time of release of the clamp the euglobulin lysis time was 26 minutes in the treated animal This diminution in the size of the infarct was the most favorable result in the treated group

The typical microscopic findings in an untreated heart are seen in Figs 5A and 5B Fibrin thrombi in minute vessels confluent necrosis of the myocardium and interstitial protein rich edema are evident In contrast Figs 6A and 6B demonstrate the pattern in a treated animal Microthrombi are absent the myocardial damage is focal rather than confluent and there is negligible interstitial edema Myocardial rupture did not occur as a result of fibrinolytic therapy nor was there an increased incidence of intramyocardial hemorrhage in the treated group In addition no other deleterious effects of the proteolytic enzyme were noted upon the uninfarcted posterior myocardial wall of these animals[1]

Tables I and II enumerate the incidence of microthrombi or blockade of small vessels by fibrin like material and the character of the myocardial damage in the treated and untreated dogs Ten of 13 control animals demonstrate microthrombi whereas microthrombi were noted in only 2 of 15 adequately treated animals The microthrombi noted in one of the animals which had been treated for 3 days were probably present as part of an unrelated arteriolar disease antedating the treatment of this animal since they appeared to be older than 3 days by microscopic criteria

Table I Incidence of thrombi in microcirculation in treated group with euglobulin lysis times shorter than 1 hour

Infarct age	*Controls*	*Treated*
12–24 hr	3/3	0 5
48 hr	1/2	1 4
3 days	4/5	1 5
4 7 days	2/3	0 1
Total	10/13	2 15

*Older th 3 days

Table II Incidence of type of necrosis in treated group with euglobulin lysis times shorter than 1 hour

Infarct ge	*Controls*		*Treated*	
	Confluent	*Focal*	*Confluent*	*Focal*
12–24 hr	3	–	1	4
48 hr	2	–	1	3
3 days	4	1	–	5
4–7 day	2	1	–	1
Total	11	2	2	13

Eleven of 13 control animals revealed only confluent necrosis whereas focal necrosis was present in 13 of the treated group and confluent necrosis alone in only 2 of these dogs This low incidence of micro thrombi and confluent necrosis in the treated animals is statistically significant

Discussion

After coronary occlusion there are extensive zones of starved myocardium surrounding areas which are irreversibly damaged Fibrinolytic therapy is one means of alleviating this starvation and returning portions of these marginal zones to anatomic and functional integrity The collateral blood supply probably plays a vital role in maintaining some nourishment at first and the intrinsic resistance of portions of the myocardial fiber to severe injury appears to be much greater than previously estimated

These studies indicate that there are large areas of myocardium that can be salvaged up to 3 hours after ischemic injury The apical and subendocardial regions appear to be most irreversibly damaged whereas the marginal areas are salvable for long periods by fibrinolytic therapy Our results show that these zones of reversible injury may constitute 25 to 50 per cent of the area of infarction expected in control animals This apparent extension of the limits of myocardial viability previously not observed after restoration of the blood supply alone appears to be the direct effect of fibrinolytic activity upon the acute ischemic tissue reaction in the heart muscle and demonstrates that the speed of muscle breakdown within an infarct area is not uniform In our studies we were impressed with the powerful influence of these enzymes upon the tissue reaction It appears logical that the use of these clot dissolvers for the lysis of major clots is not possible without profound effects at the tissue level wherever fibrin may be deposited There is an obvious need to extend the study of these enzymes to any tissue reaction associated with deposition of fibrin

We interpret the absence of micro thrombi and interstitial precipitation of



Fig 4B Spotty focal subendocardial infarction (treated)



Fig 5A Seven day control Dense mesh of interstitial fibrin and coagulated protein in infarcted zone. There are necrotic polymorphonuclear leukocytes and macrophages in the coagulum



Fig 5B Seven day control Note arteriole with organizing thrombus (right) Adjacent to the arteriole is large zone of interstitial fibrin and protein coagulum which contains necrotic exudate There are infarcted muscle fibers which are anuclear and fragmented (left lower)

protein rich edema in the hearts of treated animals in contrast to the findings in the hearts of control animals as evidence that nutrition is restored to the marginal muscle regions by maintenance of the patency of the capillary circulation and clogged tissue spaces Since all animals were heparinized before they were sacrificed these findings cannot be due to postmortem clotting Furthermore the high incidence of small focal areas of necrosis in the treated animals rather than large confluent zones indicates that reversible local changes are present such as those often seen in patients with long-standing angina pectoris rather than irreversible massive generalized deprivation We had previously postulated[7] that fibrinolytic therapy dissolved out the microblockage to the coronary circulation However analysis of the microscopic findings in a control group of dogs which died within 12 hours after infarction failed to reveal the presence of microthrombi before 6 hours Thus fibrinolytic therapy may have *prevented* this blockade rather than reversed it Whether it is necessary to render these animals hypo- or afibrinogenemic to accomplish this beneficial effect or whether some other less specific mechanism of action is important is presently under study in our laboratory

It is certain that this hypothesis of microthrombosis is an oversimplification of the many factors which govern the rate of myocardial death The small number of microthrombi we have seen in each heart is quantitatively insufficient to explain the degree of blockade of the microcirculation which we have postulated However it is possible that these microthrombi are the expression of the end result of hypercoagulability after ischemic injury and that *functional* capillary blockade occurs even prior to actual formation of microthrombi At present we are measuring the coagulability of the coronary venous blood after coronary occlusion and preliminary data indicate that a state of hypercoagulability is produced within 1 hour after ischemia of the myocardium This state can serve to perpetuate deprivation of cell nutriment at a microscopic level

These experimental results encourage the use of fibrinolytic therapy in human myocardial infarction Successful therapy within the previously accepted limits of myocardial viability of [1] hour after total ischemia is impractical if not totally impossible especially if the only aim is to dissolve an obstructing coronary thrombus It seems unlikely that total dissolution of this thrombus could be affected in less than 8 hours from the time of its formation even under optimal circumstances under clinical conditions This estimate of elapsed time includes inevitable delays in the obtaining of medical assistance transportation to the hospital organization of the treatment personnel etc as well as an estimated 4 to 6 hours necessary for actual clot lysis [11]

On the other hand the goal of restoration of the patency of the capillary circulation more quickly after myocardial infarction is logical and feasible. It seems likely that these enzymes may reach marginal zones of ischemic myocardium through collateral before the major coronary channel is reopened. That this goal may be of the utmost importance is further emphasized by the recent evidence that fresh *major* coronary thrombi are found in less than 60 per cent of the cases of sudden cardiac death.

A further drawback to clinical effectiveness may be our evidence that euglobulin lysis times of less than 1 hour seem to offer

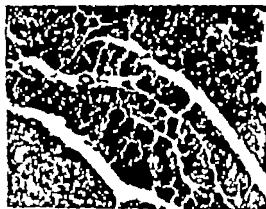


Fig. 6A. Forty-eight hour treated. Note isolated infarcted muscle fibers in center of photograph. They are darker, glossy, and anuclear. Note also clean interstitial space with no fibrin or protein debris.

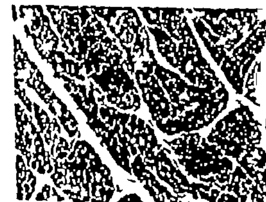


Fig. 6B. Three day treated. Note two infarcted muscle fascicles which are beginning to organize. The remaining muscle fascicles are normal; the interstitial spaces are clean. This reaction is probably the result of focal starvation of temporary nature.

optimal diminution in the size of the infarct. This intense fibrinolytic activity over a period of 6 to 12 hours may cause hemorrhagic complications with significant depletion of circulating fibrinogen and other clotting factors. Since the proportions of fibrinolysin and streptokinase utilized in this study obviously produced circulating and tissue fibrinolysis and proteolysis of intense degree but in a proportion peculiar to these particular mixtures, other types of fibrinolytically active states may produce results in the myocardium which are different from those reported here.

There was no evidence that the fibrinolytic therapy itself in the present experiments caused myocardial hemorrhage, rupture, or rheumatic-like or degenerative lesions as reported with papain or streptococcal proteinase in rabbits.[11]

Summary

1. The extent of experimental canine myocardial infarction was markedly diminished by fibrinolytic therapy.

2. This effect appeared to be the result of maintaining the patency of the microcirculation of the heart, with the salvage of ischemic marginal areas after coronary occlusion.

3. Fibrinolytic therapy extends the duration of viability of large areas of the myocardium after ischemic injury.

4. Intense fibrinolytic activity was induced to the extent of producing hemorrhagic complications in some of the animals.

5. The implications of this therapy in human myocardial infarction are discussed.

REFERENCES

1. Blumgart, H. L., Gilligan, D. R., and Schlesinger, M. J.: Experimental studies on the effect of temporary occlusion of coronary arteries, Am. Heart J. 22:374, 1941.
2. Tennant, R., Grayzel, D. M., Sutherland, F. A., and Stringer, S. W.: Studies on experimental coronary ligation, Am. Heart J. 12:168, 1936.
3. Nam, S. A., and Lewis, F. J.: Profound hypothermia in the monkey with recovery after long periods of cardiac standstill, J. Appl. Physiol. 10:137, 1957.
4. Webb, W. R., and Howard, H. S.: Extension of the limits of cardiac viability with total coronary occlusion, Surgery 42:92, 1957.
5. Kardesch, M., Hogancamp, D. E., and Bing, R. J.: The survival of excitability, energy

production and energy utilization of the heart Circulation 18 935 1958
6 Benson E S Halloway B E and Turbak C E Contractile properties of glycerol-extracted muscle bundles from the chronically failing canine heart Circulation Res 6 122 1958
7 Ruegsegger P Nydick I Hutter R C Freiman A Bang N U Clifton E E and LaDue J Fibrinolytic (plasmin) therapy of experimental coronary thrombi with alteration of the evolution of myocardial infarction Circulation 19 7 1959
8 Clifton E E and Cannamela D A Fibrinolytic and proteolytic activity of human plasminogen prepared from fraction III of *human plasma J Appl Physiol* 6 42 1953
9 Freiman A H Bang N U and Clifton E E Studies on the production of intravascular thrombi and their treatment with fibrinolysin Circulation Res 8 409 1960
10 Weinberg A Personal communication
11 Kellner A and Robertson T Myocardial necrosis produced in animals by means of crystalline streptococcal proteinase J Exper Med 99 495 1954
12 Sherry S and Alkjaersig N Biochemical experimental and clinical studies of proteolytic enzymes with particular reference to the fibrinolytic enzyme of human plasma Ann New York Acad Sc 68 52 1957
13 Nydick I Ruegsegger P Abarquez R Clifton E F and LaDue J S The effect of fibrinolytic agents on myocardial infarction *Prog Cardiovas Dis* 3 13 1960

The influence of high altitudes on the electrical activity of the heart

Electrocardiographic and vectorcardiographic observations in adolescence and adulthood

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That right ventricular preponderance is a frequent electrocardiographic finding among healthy residents of high altitudes was first observed in Bolivia by Capdehourat. Rotta[2] found signs of right ventricular hypertrophy and right bundle branch block in the native residents of high altitudes of Peru. Cosio and Corigliano[3] studied at sea level subjects who came from high altitudes and confirmed the above mentioned findings. The electrocardiograms observed in the adult residents of high altitudes were classified by Rotta and Lopez[4] into four groups similar to those described by Taquini[5] in chronic pulmonary heart disease. The present work has been carried out in order to investigate the genesis of such variable electrocardiograms. It complements a previous study made in children.[6]

It should be remembered that a moderate arterial oxygen unsaturation, polycythemia, increased pulmonary blood volume, and mild pulmonary hypertension are common findings in healthy people who live permanently at high altitudes.[7-11] These findings are physiologic characteristics in such a low pO_2 environment. Adaptive mechanisms in pulmonary function, blood chemistry, and enzymatic activity are also present in the residents of high altitudes who are capable of efficiently performing heavy exercise.[12]

Material and methods

Three hundred normal subjects were studied in Lima, at sea level, and 250 in Morococha, 14,900 feet (4,540 meters) above sea level. The individuals were distributed in three age groups: 15 to 20 years (100 subjects at sea level and 50 at high altitudes), 21 to 40 years (100 subjects at both levels), and 41 to 60 years (100 subjects at both levels). Male and female subjects in equal proportion were included in each age group. The residents of high

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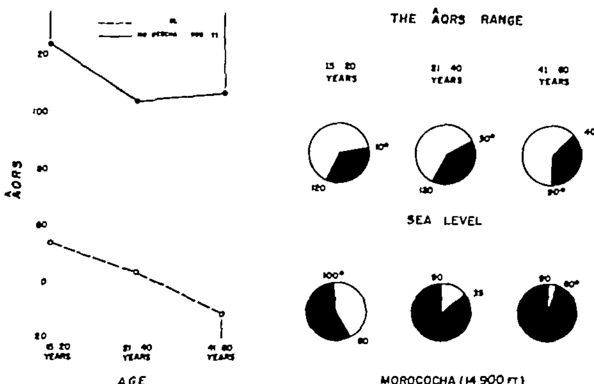


Fig 1 A right ÂQRS deviation is common finding in healthy people who live permanently at high altitudes (*left*) As their age increases the ÂQRS range is wider at high altitudes and in older adults ÂQRS can be found in any one of the Bayley sextants (*right*)

altitudes had lived 5 years without interruption in Morococha and had always lived at altitudes above 10 000 feet

A Sanborn Viso Cardiette Model 52 electrocardiograph was used Conventional leads and additional chest leads were taken in each subject The vectorcardiograms were recorded according to Grishman s cube method[14] based on a modification of the trirectangular trihedron of Duchosal and Sulzer[15] A Sanborn Vector Amplifier Model 185 coupled to a Sanborn Viso Scope Model 169A and a Polaroid Fairchild camera Model F 296A were employed The vector loop was interrupted 400 times per second by intensity modulations

Results

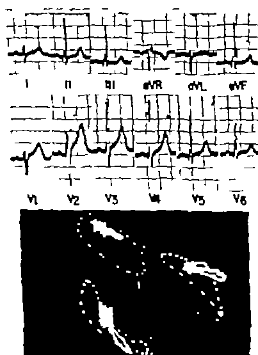
Ventricular activation process

STATISTICAL ANALYSIS Tables I II and III show the statistical analysis of the data concerning the ventricular activation process at sea level and at high altitudes The difference between the mean values of ÂQRS obtained at sea level and those at high altitudes was statistically significant ($p < 0\,001$) in all age groups (Table I) showing a right ÂQRS deviation at high altitudes (Fig 1 *left*) However as the *age of the subjects increased the ÂQRS* range was wider at high altitudes and in older adults the ÂQRS was in any one of the Bayley sextants (Fig 1 *right*) Table II shows the voltage of the late R wave in Lead aV_R and the R/Q or S ratio in the same lead The mean values at high altitudes were greater than and showed a statistically significant difference from those at sea level Table III shows the voltage of the R wave and the R/R + S ratio in Lead V_1 The mean values were significantly greater at high altitudes in the adolescent group only At high altitudes the values for the R/S ratio in Lead V_6 were lower and the index R in Lead V_1 + S in Lead V_6 showed higher values The difference between the mean values obtained in the two places studied is highly significant in all age groups

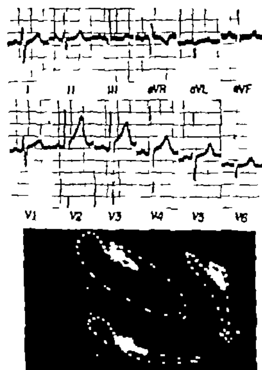
ELECTROCARDIOGRAPHIC AND VECTORCARDIOGRAPHIC PATTERNS In adult dwellers of high altitudes there was a wide range in SÂQRS direction the configura

tion of the QRS complex was highly variable both in the limb and precordial leads and the two-dimensional projections of the spatial QRS loop showed wide diversity. In order to systematize our results we will describe five principal patterns according to the spatial SÂQRS orientation. In this way we do not prejudge differences in the ventricular activation process.

1. SÂQRS in the right inferior posterior octant. SÂQRS was directed to the right, inferiorly, and somewhat posteriorly in most of the adult inhabitants of high altitudes (38.4 per cent). This SÂQRS position was a vectorial resultant of two portions differently oriented but approximately similar in magnitude (Fig. 2). The mid QRS vectors (QRS loop 2 or "left ventricular vectors"[16]) were directed to the left, downward, and somewhat anteriorly. The late QRS vectors (QRS loop 3 or "basal vectors") were large and pointed to the right, upward, and posteriorly. The former showed their major projection on the frontal and horizontal planes and the latter on the sagittal view. The early QRS vectors (QRS loop 1 or "septal vectors") were small and anteriorly oriented whether to the left or to the right. The frontal QRS loop was wide and showed a clockwise rotation. The horizontal QRS loop was narrow and approximately perpendicular to the axis of Lead X, and it was inscribed in a clockwise direction or in a figure of eight. $S_1Q_2Q_3$ or $S_1S_2Q_3$ patterns and an rS complex in Lead V_1 were frequently found in these residents of high altitudes.



A



B

Fig. 2. *A*. A normal 23 year-old subject who lives at high altitudes. SÂQRS is in the right inferior posterior octant and its frontal projection is oriented to +9. The QRS loop is wide in the frontal view and clockwise rotation is seen in all three planes. The mid and final QRS vectors are approximately similar in magnitude. In this subject the following additional data were obtained: right ventricular systolic pressure 43 mm Hg, hemoglobin 22 Gm. per cent, hematocrit 60 per cent, arterial oxygen saturation 82 per cent. *B*. A normal 22 year-old inhabitant of high altitudes. SÂQRS is in the right inferior posterior octant and its frontal projection is placed at +115. The QRS loop is wide in the frontal plane and narrow (in profile) in the transverse view, which shows figure-of-eight rotation.

Some subjects showed an rsr s' complex of low voltage and normal duration in Lead V_1 In some subjects (3 6 per cent) a peculiar projection of the mid and late QRS vectors made it impossible to determine the ÂQRS position and diphasic QRS complexes were observed in all six extremity leads (Fig 3 *A*)

2 SÂQRS in the left inferior posterior octant This pattern was found in 25 2 per cent of the residents of high altitudes In these individuals the spatial QRS loop was somewhat similar to that described in the previous group but the frontal projection of the late QRS vectors was small (Fig 4 *A*) In some subjects of this group rsr's complexes of low voltage and normal duration were found in Lead V_1 (Fig 3 *B*) In a few cases (2 8 per cent) SÂQRS was in the left inferior anterior octant and an *Rs* pattern was seen in Lead V_1 (Fig 4 *B*)

Table I The ÂQRS position

		15 20 year	21–40 years	41 60 years
Sea level	Mean ± SE	55 ± 2 2	45 ± 3 3	50 ± 3 3
	SD	22 3	32 4	37 7
	Extreme Values	−10 120	−30 120	−40 90
Morococha (14 900 ft.)	Mean ± SE	123 ± 6 8	105 ± 7 1	108 ± 7 9
	SD	46 1	70 2	78 5
	Extreme Values	60 −100	−35 −90	−80 −90
t		12 31	7 77	9 08

t values calculated by Fisher t test.
*p < 0 001

Table II The QRS scalar data in Lead aVR

		15 20 years	21–40 years	41 60 years
R in aVR (in mm = 0 1 mv)				
Sea level	Mean ± SE	1 1 ± 0 12	0 7 ± 0 09	0 5 ± 0 07
	SD	1 16	0 96	0 69
	Extreme Values	0 5	0 5	0 3 5
Morococha (14 900 ft)	Mean ± SE	4 0 ± 0 32	2 8 ± 0 24	2 9 ± 0 18
	SD	2 24	2 35	1 82
	Extreme Values	1 10	0 11	0 8
t		10 59	8 44	12 95
R / Q or S in aVR				
Sea level	Mean ± SE	0 2 ± 0 02	0 1 ± 0 02	0 1 ± 0 01
	SD	0 19	0 20	0 14
	Extreme Values	0 1	0 1 2	0 0 7
Morococha (14 900 ft)	Mean ± SE	1 1 ± 0 16	0 8 ± 0 09	0 9 ± 0 11
	SD	1 13	0 99	1 09
	Extreme Values	0 1 7 0	0 5	0 2 5
t		8 30	6 72	7 71

t t values calculated by Fisher t test.
*p < 0 001

Table III *The QRS scalar data in precordial leads*

Lead	Group		15-20 years	21-40 years	41-60 years
R in V (in mm = 0.1 mv)	Sea level	Mean ± SE	3.8 ± 0.24	3.3 ± 0.19	2.2 ± 0.11
		SD	1.40	1.92	1.18
		Extreme Values	0 13	0 16	0 6
	Morococha (14,900 ft)	Mean ± SE	6.3 ± 0.56	3.5 ± 0.23	2.3 ± 0.15
		SD	4.01	2.38	1.52
		Extreme Values	1 23	0 12	0 7
	t		4.90	0.87	0.36
$\frac{R}{R+S}$ in V	Sea level	Mean ± SE	0.3 ± 0.01	0.3 ± 0.01	0.3 ± 0.01
		SD	0.13	0.14	0.14
		Extreme Values	0 0.7	0 0.6	0 0.6
	Morococha (14,900 ft)	Mean ± SE	0.4 ± 0.03	0.3 ± 0.02	0.2 ± 0.02
		SD	0.19	0.20	0.17
		Extreme Values	0.1 0.8	0 1	0 0.8
	t		5.17	0.53	0.35
$\frac{R}{S}$ in V	Sea level	Mean ± SE	5.5 ± 0.55	8.3 ± 0.9	12.8 ± 1.24
		SD	5.44	6.76	9.0
		Extreme Values	0.5 20	1 42	1.7 42
	Morococha (14,900 ft)	Mean ± SE	2.0 ± 0.23	3.4 ± 0.31	2.9 ± 0.29
		SD	1.61	3.05	2.94
		Extreme Values	0.5 9	0.1 16	0.4 11
	t		4.42	4.8[illegible]	9.38
R in V + S in V	Sea level	Mean ± SE	8.1 ± 0.38	5.2 ± 0.28	3.1 ± 0.16
		SD	3.79	2.79	1.60
		Extreme Values	2 18	0.5 19	0.5 7
	Morococha (14,900 ft)	Mean ± SE	13.7 ± 0.77	8.8 ± 0.47	7 ± 0.39
		SD	5.45	4.70	3.98
		Extreme Values	11 28	1 26	2 30
	t		7.30	6.61	10.8

t [illegible] calculated by F[illegible] test
$p < 0.001$

3 SÂQRS in the right superior posterior octant the $S_1 S_2 S_3$ pattern In some adult dwellers of high altitudes (9.6 per cent) SÂQRS and the major portion of the spatial QRS loop were directed to the right superiorly and posteriorly (Fig 5 *A*) In these subjects the late QRS vectors (QRS loop 3 or basal vectors) were predominant The early QRS vectors were small and anteriorly oriented whether to the left or to the right The mid QRS vectors were also small The frontal QRS loop was inscribed in a counterclockwise direction or in a figure of eight The rotation of the horizontal QRS loop was in a clockwise fashion with the mid QRS

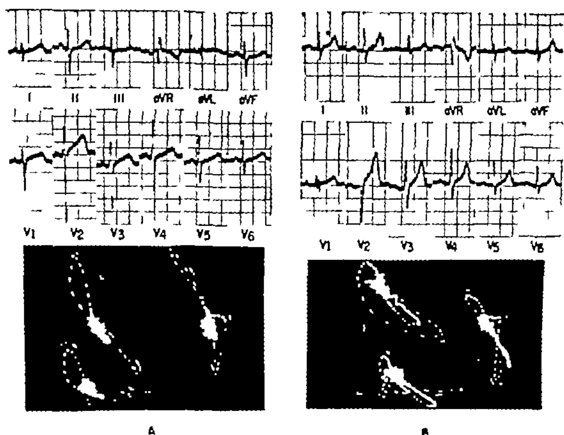


Fig. 5. A, A normal 25 year-old resident of high altitudes. ÂQRS is undetermined and diphasic QRS complexes are present in all six limb leads. The QRS loop shows a figure-of-eight configuration in the transverse projection and the final QRS vectors are of great magnitude. B, A healthy 35 year-old resident of high altitudes. ÂQRS points to the left. The final QRS vectors are large. The frontal QRS loop is wide and shows a clockwise rotation. An rsr' pattern is present in Lead V_1 and the horizontal QRS loop rotates in a figure of eight.

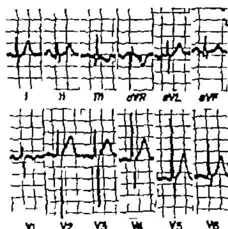
vectors anteriorly oriented or in a figure of eight, and the mid QRS vectors posteriorly directed. An rS pattern was frequently found in all three standard limb leads ($S_1 S_2 S_3$ pattern or "concordant S pattern") and in all six unipolar precordial leads.

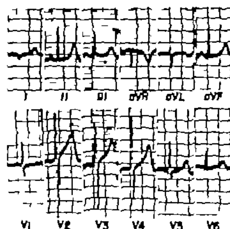
4. SÂQRS in the left superior posterior octant. In these subjects (6.4 per cent) SÂQRS and the major portion of the spatial QRS loop were oriented to the left superiorly and posteriorly (Fig. 5 B). The QRS loop was similar to that of the previous group but the mid QRS vectors were large and the final QRS vectors were only slightly oriented to the right. The inscription of the horizontal QRS loop was counterclockwise or in a figure of eight. The morphology of the QRS complex was also similar to that of the previous group, but diphasic or predominantly positive QRS complexes were frequently seen in Leads I and V_6.

5. SÂQRS in the right inferior anterior octant. In some residents of high altitudes (8.0 per cent), particularly those of the adolescent group, SÂQRS and the major portion of the spatial QRS loop were directed to the right, inferiorly, and anteriorly (Fig. 6 A). Vectors pointing in this direction ("right ventricular vectors") were predominant, whereas the left QRS vectors and the late QRS vectors were relatively small. The early QRS vectors were small and anteriorly directed, frequently to the left. The frontal and horizontal QRS loops were wide and inscribed in a clockwise direction. The configuration of the QRS complex in the extremity leads was similar to the one described in the first pattern. The QRS complex in Lead V_1 was predominantly

positive and the most frequent configuration was Rs with an early slurring in some cases. QRS complexes of rsR's, rR's and qRs morphology were also seen in Lead V_1 and in the right additional chest leads. This diverse configuration was related to the variable orientation of the first portion of the QRS loop. A final S wave was a constant finding in Lead V_1 in residents of high altitudes. In some subjects (6.0 per cent) the increased right ventricular vectors were associated with large final QRS vectors (Fig. 6 *B*). In these cases SÂQRS and the spatial QRS loop were in the right superior anterior octant, and $S_1S_2S_3$ or $S_1S_2Q_3$ patterns were associated with predominantly positive QRS complexes in Lead V_1.

Ventricular repolarization process. The adolescents and adults living at high altitudes showed a leftward anterior inferior orientation of the T loop and positive T waves in all precordial leads. Significant divergence between the QRS and T loops and a left posterior displacement of the J point ("secondary" ST-T changes) were not observed despite the right anterior position of the QRS loop seen in some cases (Fig. 6 *A*). The upright T waves of the right precordial leads were abnormal in contour in approximately 20 per cent of the subjects in high altitudes. In some cases the T loop was in the left posterior inferior octant and the T waves were negative, peaked, and symmetrical ("primary" T wave changes) in the right







A



B

Fig. 4. *A*, A 28-year-old resident of high altitudes. SÂQRS is in the left inferior posterior octant and its frontal projection points to + 0. The QRS morphology differs *only slightly from* that observed in normal adults at sea level. However, the frontal QRS is wide and a clockwise rotation is seen in all three planes. The horizontal QRS loop shows two well-defined portions. *B*, A normal 31-year-old subject who lives at high altitudes. SÂQRS is in the left inferior anterior octant. The QRS configuration is normal in the limb leads and an Rs complex is seen in Lead V_1. The horizontal QRS loop is anteriorly placed and shows counterclockwise rotation. The final QRS vectors are small. In this subject the right ventricular systolic pressure was 37 mm. Hg, hemoglobin was 21 Gm. per cent, hematocrit was 62 per cent, and arterial oxygen saturation was 81 per cent.

precordial leads (Fig. 5,*A*). A comparison of downward T waves in the right precordial leads at sea level and those at high altitudes is shown in Table IV. Negative T waves in Lead V_1 were found less frequently with increasing age of the subjects at sea level. They were rare in Lead V_2 and were not observed in Lead V_3. At high altitudes a negative T wave was an infrequent finding in Lead V_1, but in those subjects who showed an "ischemic" T wave pattern, negative T waves were also seen in Leads V_2 and V_3.

Discussion

Ventricular adaptation process. A considerable delay in the development of the QRS changes that normally occur during growth has been demonstrated in infants and children who live permanently at high altitudes. In comparison with children, the adult dwellers at high altitudes show less right ÂQRS deviation, the mid QRS vectors are larger and show a less forward orientation, and the early QRS vectors are more frequently directed to the right. These vector changes indicate that as the age of the subject increases, the right ventricular preponderance diminishes. However, it occurs slowly and physiologic preponderance of the left ventricle is not attained at high altitudes.

Electrocardiographic and vectorcardiographic patterns are almost stereotyped in infancy and childhood at high altitudes and SÂQRS is generally in the right anterior octants.[4] On the other hand, the ECG and VCG patterns are highly variable in adult inhabitants of the same altitudes. In most subjects the spatial orientation of the mid QRS vectors and the pathway of the horizontal QRS loop show similarities to those observed at sea level in transitional patterns of normal children between 3 months and 3 years of age.[4] However, at high altitudes the final QRS vectors are of great magnitude, which accounts for the rS complex in Lead V_1 and the SÂQRS position in the right inferior posterior octant. Patterns of this group are similar to Grishman's Type I described in some congenital heart diseases with a mild right ventricular hypertension,[7,8] and they also resemble De Glaude's Types I and II reported in mitral stenosis with a mild pulmonary hypertension.[18] However, the late QRS vectors are usually of greater magnitude in healthy residents of high altitudes, and for this reason an rS pattern in Lead V_1 is more frequently found in these subjects than in persons with mitral stenosis or congenital cardiac malformations. At high altitudes these patterns are associated with a mild right ventricular hypertension, and they should be considered as one type of systolic overloading of the right ventricle in spite of the rS or rsr's complexes in Lead V_1.

In residents of high altitudes who show SÂQRS in the left inferior posterior octant, the electrocardiogram resembles that seen in normal adults at sea level, but the vectorcardiogram differs only slightly from that described in the previous pattern. This singular finding in the presence of right ventricular hypertrophy has been rarely reported.[19] The pattern of SÂQRS in the left inferior anterior octant and an Rs complex in Lead V_1 resembles that frequently observed at sea level in normal children up to 3 years of age.[4] SÂQRS

Table IV. Distribution in per cent of the negative T waves in the right precordial leads

	Sea level			Morococha (14,900 ft.)		
	15-20 years (%)	21-40 years (%)	41-60 years (%)	15-20 years (%)	21-40 years (%)	41-60 years (%)
Lead V_1	58	23	13	22	8	8
Lead V_2	1	1	0	8	5	3
Lead V_3	0	0	0	6	0	2

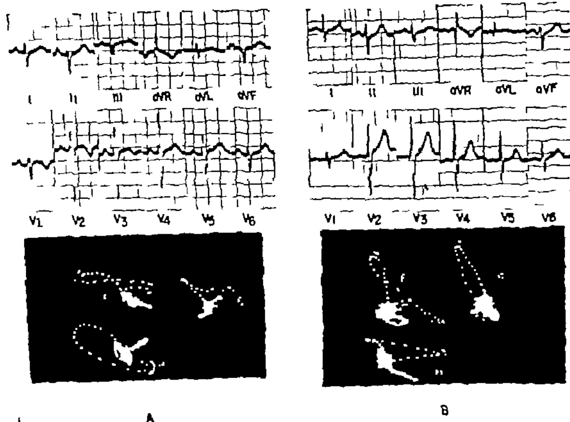


Fig 5 *A* A normal 27 year-old d ller t high altitudes SÂQRS is in the right superior posterior octant nd its frontal projection points to −120 An S_1 S_2-S_3 pattern is present An rS complex is seen in all ix precordial leads The final QRS vectors are predominant The frontal QRS loop exhibits a figure-of-eight rotation nd the horizontal QRS loop rotates clockwise w th the mid QRS ectors oriented anteriorly An ischemic T ve pattern is seen in the right precordial lead I this subject the right ventricula sy tolic pre ure was 42 mm Hg hemoglobin was 21 Gm per cent hematocrit was 61 per cent and rterial oxygen saturation as 82 per cent *B* A normal 58 year-old inhabitant of high altitudes SÂQRS is in the left superior po terior octa t nd its frontal projection is oriented to −75 The QRS configuration is similar to that seen in *A* but Rs complex is present in Lead I and n the left precordial leads The final QRS vectors re predominant but they are only slightly oriented to the right The QRS-loop rotation is counterclockwise i the transverse projection nd figure of eight in the frontal iew

orientation in the left superior *posterior* octant is observed in older adults and in subjects who li ed the greater part of their lives n altitudes lower than that of Morococha Similar patterns in the presence of right ventricular hypertrophy have been rarely reported in chronic cor pulmonale[8] and in some congenital heart diseases

Electrocardiographic and vectorcardiographic patterns associated with SÂQRS in the right superior posterior octant have also been described in chronic pulmonary heart disease and in some congenital cardiac malformations[7, 31] They are similar in some respects to Grishman s Type III reported in some congenital heart diseases with severe right ventricular hypertension[7] However in most of Grishman s cases SÂQRS was oriented anteriorly and positive QRS complexes were present in Lead V_1 In our residents of high altitudes an rS complex in Lead V and a mild right ventricular hypertension were common findings The electrogenesis of the S_1 S_2-S_3 syndrome has been extensively discussed and frequently it was ascribed *to a* marked clockwise rotation of the heart around its longitudinal axis with posterior displacement of the apex[27, 34]

In recent paper from Grishman [illegible] pattern has been [illegible] d ded in th Type II

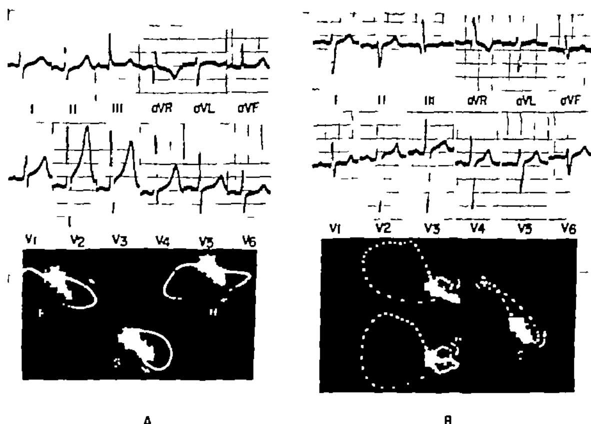


Fig. 6. A, A 22-year-old healthy resident of high altitudes. SÂQRS is in the right inferior anterior octant. The right precordial leads show positive QRS complexes and positive T waves. The frontal and horizontal QRS loops are wide and rotate in a clockwise direction. In this subject the right ventricular systolic pressure was 50 mm. Hg, hemoglobin was 23 Gm. per cent, hematocrit was 66 per cent, and arterial oxygen saturation was 79 per cent. B, A healthy 20-year-old resident of high altitudes. SÂQRS is in the right superior anterior octant. The right QRS vectors and the final QRS vectors are large. An S_1 S_2-S_3 pattern is present and Lead V[illegible] shows a QRS complex with a late R wave (qRs configuration).

The vectorial observations[illegible] and the epicardial leads in man[illegible] have shown in these cases an unusual sequence of ventricular activation in which the late QRS vectors are predominant. In our subjects the large projection of the late QRS vectors in all three planes does indicate a true spatial increase of these vectors. For this reason we cannot consider that a special position of the heart is an important determining factor of such a pattern. Furthermore, the roentgen examination and the anatomic study do not disclose any peculiarities in the heart position in subjects with this pattern. Special changes in the tissues surrounding the heart which might explain these bizarre cases by modifications of the conducting media were not apparent in these subjects. The S_1 S_2-S_3 pattern seen in some healthy people who live permanently at high altitudes should be considered as another type of systolic overloading of the right ventricle in spite of the rS complex in Lead V_1.

The pattern associated with SÂQRS in the right inferior anterior octant resembles one type described by Cabrera in systolic overloading of the right ventricle,[illegible] some examples of Grishman's Type II,[illegible] and Deglaude's Types III and IV.[illegible] However, in cases reported by these and other authors the QRS pattern was frequently associated with secondary ST-T changes and was seen in the presence of accentuated right ventricular hypertrophy,[illegible] with the ventricular systolic pressure similar to or higher than that of the systemic circulation.[illegible] However, in healthy people who live permanently at high altitudes this QRS pattern is not associated with

secondary ST T changes and is found in the presence of only a mild right ventricular hypertension This pattern is similar to that seen in infants and children of the same altitudes [4] and its persistence until adult age suggests that a mild right ventricular hypertension if maintained throughout infancy and childhood can arrest to an important degree the normal pattern of development of the QRS changes expected with aging The same explanation is probably valid for the presence of marked signs of right ventricular preponderance in some congenital heart diseases with a mild right ventricular hypertension [41 1] This however does not occur when the right ventricular hypertrophy is acquired after the normal left ventricular preponderance has been attained for example in chronic cor pulmonale and mitral stenosis In these cases a high degree of right ventricular pressure is required in order to produce accentuated signs of right ventricular hypertrophy [41 11]

The five mentioned QRS patterns do not represent different types of ventricular activation They are rather varieties of a peculiar ventricular activation process which exhibits two principal characteristics an increased magnitude of the terminal QRS vectors and a delay in the development of the QRS changes expected with aging The association in variable proportion of these two features could explain the variable electrocardiograms and two dimensional vectorcardiograms observed in adolescence and adulthood at high altitudes Rotta and Lopez[1] described four electrocardiographic patterns in normal adult inhabitants of high altitudes The pattern reported as right ventricular hypertrophy is similar to the one described by us in which S$\hat{A}$QRS is in the right anterior octants The pattern suggestive of right ventricular hypertrophy corresponds to S S-S syndrome and it is ascribed by the above mentioned authors to positional changes of the heart Their normal pattern is similar to that described by us in which S$\hat{A}$QRS is in the left inferior posterior octant but we did not find normal vectorcardiograms in the residents of high altitudes of this group The pattern with S$\hat{A}$QRS in the right inferior posterior octant the most common in adults of high altitudes is not commented upon by these authors A pattern with S$\hat{A}$QRS in the left superior posterior octant was not studied Right bundle branch block incomplete or complete is the fourth pattern pointed out by these authors and it will be discussed later This classification implies different types of ventricular activation and it ascribes an important role to the cardiac position in the genesis of the electrocardiograms at high altitudes The results of our investigation are not in agreement with this hypothesis

Complete right bundle branch block was a rare finding in normal dwellers of high altitudes An R R complex of normal duration and low voltage frequently of rsr's configuration was found in Lead V_1 in 8 5 per cent of the subjects studied at high altitudes This pattern probably represents a transitional stage in the pattern of development of QRS changes throughout life Various features support this hypothesis (1) An r V transitional pattern can be seen in normal children who live at sea level whereas at high altitudes the same pattern is not found until adult age On the other hand native residents of high altitudes with an Rs pattern in Lead V show the r' V pattern after one or more years of residence at sea level [4] This phenomenon resembles that reported after operation in certain heart diseases with right ventricular hypertrophy [41 47] (2) The final portion of the QRS loop does not show the characteristics commonly seen in clinical and experimental right bundle branch block [41] (3) The intracavity leads of the right ventricle recorded as recommended by Sodi Pallares and associates [4 41] are frequently normal in subjects with an r' V_1 pattern at high altitudes [4] As for the R V_1 pattern with a predominantly positive QRS complex (rsR s rR s or qRs configurations) seen in some subjects who live at high altitudes this is probably related to the association of right ventricular hypertrophy and a certain degree of right bundle branch block [41]

Ventricular repolarization process The greater frequency of positive T waves in the right precordial leads at high altitudes is probably related to chronic right ventricular overloading as is seen in infancy

and childhood.[4,44,46] The ischemic T wave pattern seen in the right precordial leads of some residents of high altitudes is also frequently observed in newcomers to these places[44,47] and in natives who lose their adaptation to high altitudes.[1] In these subjects the ischemic T wave pattern is related to subacute right ventricular overloading. When this pattern appears in normal residents of high altitudes it probably constitutes an early index of disadaptation to high altitudes.

The right ventricular hypertrophy of high altitudes and its relation to the mechanisms of acclimatization. Electrocardiographic and vectorcardiographic characteristics of the people who live permanently at high altitudes are associated with a moderate increase in the weight of the right ventricle; the thickest portion of the right ventricular wall is the outflow tract,[39] which agrees with the increased magnitude of the late QRS vectors. A mild pulmonary hypertension and a normal cardiac output have been found in the same subjects.[31] After birth the hypoxia of high altitudes maintains the fetal structure of the small pulmonary arteries and arterioles[43] and as a consequence an elevated pulmonary vascular resistance and a mild pulmonary hypertension are also maintained. Polycythemia, an early adaptive hematological mechanism, and an increased pulmonary blood volume[2] probably also contribute to the increase of pulmonary vascular resistance and pulmonary pressure. The pulmonary hypertension maintained throughout life explains the peculiar characteristics of the electrical activity of the heart at high altitudes: a delay in the pattern of development of the QRS changes with aging, an increased magnitude of the terminal QRS vectors, and a high incidence of positive T waves in the right precordial leads.

The electrocardiograms and vectorcardiograms of the adolescent and the adult who live permanently at high altitudes are not similar to those of the normal adolescent and adult at sea level. The electrocardiographic measurements show statistically significant differences between the two places. Therefore, a high altitude environment is an important cause of electrocardiographic and vectorcardiographic variability in healthy people. It is important to remember this in evaluating the electrocardiographic and vectorcardiographic findings in heart diseases at high altitudes.[3]

Summary

1. Electrocardiographic and vectorcardiographic observations were obtained in 550 normal subjects, 300 at sea level and 250 in Morococha, 14,900 feet above sea level. A comparative study was made in three age groups; the age range was 15 to 60 years.

2. The ventricular activation process shows significant differences between the two places studied. In adolescent and adult inhabitants of high altitudes there is a wide range in SÂQRS direction, the configuration of the QRS complex is highly variable both in the limb and precordial leads, and the two-dimensional projections of the spatial QRS loop show wide diversity.

3. Five principal QRS patterns are described according to the spatial SÂQRS orientation. These patterns do not represent different types of ventricular activation. They are varieties of a peculiar activation process which exhibits two principal characteristics: a delay in the pattern of development of the QRS changes that normally occur with aging, and an increasing magnitude of the terminal QRS vectors.

4. The most common pattern in adults of high altitudes shows SÂQRS in the right inferior posterior octant, an rS complex in Lead V_1, and $S_1Q_2Q_3$ or $S_1S_2Q_3$ patterns in extremity leads. The $S_1S_2S_3$ pattern is also observed and it is related to predominant late QRS vectors and not to a special cardiac position. Predominantly positive QRS complexes in Lead V_1 are infrequent in adults of high altitudes. The rSr' V_1 pattern seen in some subjects who live at high altitudes probably represents a transitional stage in the pattern of development of QRS throughout life.

5. In adults at high altitudes right ventricular preponderance is less than in children at the same altitudes, but the physiologic preponderance of the left ventricle seen at sea level does not occur even in the older adults. The moderate right ventricular hypertrophy of high altitudes

is probably related to anatomic and functional changes that take place in the pulmonary circulation as a consequence of the process of acclimatization

6 The electrocardiographic and vectorcardiographic characteristics of the adolescents and adults who live permanently at high altitudes are not similar to those of normal adolescents and adults who live at sea level Therefore a high altitude environment is an important cause of electrocardiographic and vectorcardiographic variability in healthy people

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REFERENCES

1 Capdehourat E L Estudios sobre la biologia del hombre de la altitud Buenos Aires 1937 Ministerio de Justicia e Instrucción Publica
2 Rotta A Physiologic conditions of the heart in the natives of high altitude Am Heart J 33 669 1947
3 Cosio G and Conigliano J Compromiso ventricular derecho en mineros de altura Rev peruana cardiol 5 75 1956
4 Rotta A and Lopez A Electrocardiographic patterns in man at high altitudes Circulation 5 719 1959
5 Taquini A C El corazon pulmonar Buenos Aires 1954 Editorial El Ateneo
6 Penaloza D Gamboa R Dyer J Echevarria M and Marticorena E The influence of high altitudes on the electrical activity of the heart I Electrocardiographic and vectorcardiographic observations in the newborn infants and children Am Heart J 59 111 1960
7 Hurtado A and Aste Salazar H Arterial blood gases and acid base balance at sea level and at high altitudes J Appl Physiol 1 304 1948
8 Hurtado A Merino C and Delgado E Influence of anoxemia on the hemopoietic activity Arch Int Med 75 784 1945
9 Reynafarje C Lozano R and Valdivieso J The polycythemia of high altitudes iron metabolism and related aspects Blood 14 433 1959
10 Monge C Cazorla A Whittembury G Sakata Y and Rizo-Patron C A description of the circulatory dynamics in the heart and lungs of people at sea level and at high altitude by means of the dye dilution technique Acta physiol latinoam 6 15 1956
11 Rotta A Canepa A Hurtado A Velasquez T and Chavez R Pulmonary circulation at sea level and at high altitudes J Appl Physiol 9 328 1956
12 Hurtado A Velasquez T Reynafarje C Lozano R Chavez R Aste Salazar H Reynafarje B Sanchez C and Munoz J Mechanisms of natural acclimatization Studies on the native resident of Morococha Peru at an altitude of 14 900 feet Report to the U S A F School of Aviation Medicine 1956
13 Reynafarje B Estudios de quimica tisular en la hipoxia Simposios y Conferencias XXI Congreso Internacional de Ciencias Fisiologicas Buenos Aires 1959
14 Grishman A Borun E R and Jaffe H L Spatial vectorcardiography I Technique for the simultaneous recording of the frontal sagittal and horizontal projections Am Heart J 41 438 1951
15 Duchosal P W and Sulzer R La vectocardiographie Basel 1949 S Karger
16 Penaloza D and Tranchesi J The three main vectors of the ventricular activation process in the normal human heart I Its significance Am Heart J 49 51 1955
17 Grishman A and Scherlis L Spatial vectorcardiography Philadelphia 1952 W B Saunders Company
18 Lasser R P Borun E R and Grishman A Spatial vectorcardiography right ventricular hypertrophy as seen in congenital heart disease Am Heart J 42 370 1951
19 Donoso E Sapin S O Braunwald E and Grishman A A study of the electrocardiogram and vectorcardiogram in congenital heart disease II Vectorcardiographic criteria for ventricular hypertrophy Am Heart J 50 674 1955
20 Deglaude L and Laurens P Étude vectographique de la surcharge ventriculaire droite dans le retrécissement mitral Arch mal coeur 48 129 1955
21 Zuckermann R Cabrera E Fishleder B L and Sodi Pallares D Electrocardiogram in chronic cor pulmonale Am Heart J 35 421 1948
22 Burstein J and Ellenbogen L Electrocardiograms in which the main initial ventricular deflections are directed downward in the standard leads Am Heart J 16 165 1938
23 Wilburne M and Langendorf R Significance of the electrocardiogram with prominent S waves in leads I II and III J Lab & Clin Med 28 303 1942
24 Schwartz S P and Marcus J The electrocardiogram in pulmonary tuberculosis Am Rev Tuberc 46 35 194
25 Goldberger E and Schwartz S P Electrocardiograms in which the main ventricular deflections are directed downward in the standard leads Am Heart J 29 62 1945
26 Goldberger E and Schwartz S P Electrocardiograms in chronic pulmonary disease Am Rev Tuberc 53 34 1946
27 Fenichel J and Baker L Clinical analysis of the S wave pattern electrocardiogram Am Heart J 35 106 1948
28 Caroneo G Tiltmant J and Lenegre J Signification des ondes S_1 S_2 et S_3 predominantes Arch mal coeur 42 418 1949
29 Donzelot E Metianu C Durand M and Vlad P L'axe electrique moyen de QRS dans le dernier sextant (−150 à −90) chez les congenitaux (étude de 30 cas) Arch mal coeur 43 203 1950

30 Levinthal J and Purdy A Electrocardiograms with deep S waves in all three standard leads Am J Dis Child 81 59 1951
31 Lasser R P and Grishman A Vectorcardiograms obtained in patients with right ventricular hypertrophy whose electrocardiograms display an unusual axis deviation or left axis deviation IV AM HEART J 41 901 1951
32 Gardberg M and Ashman R The QRS complex of the electrocardiogram Arch Int Med 72 210 1943
33 Wilson F N Johnston F D Rosenbaum F F Erlanger H Kossmann C E Hecht H H Cotrim N Menezes de Oliveira R Scarsi R and Barker P S The precordial electrocardiogram AM HEART J 27 19 1944
34 Goldberger E Unipolar lead electrocardiography and vectorcardiography Philadelphia 1953 Lea & Febiger
35 Grant R P Clinical electrocardiography The spatial vector approach New York 1957 McGraw Hill Book Company Inc
36 Barbato E Pileggi F Debes A C Fujioka T Magalhaes M S Tranchesi J San Juan E and Decourt L Study of the sequence of ventricular activation and the QRS complex of the normal human heart using direct epicardical leads AM HEART J 55 867 1958
37 Barbato E Debes A C Pileggi F Fujioka T Paula Silva P and Décourt L Diaphragmatic juxtacardiac leads their value in the study of the spread of activation and the QRS complex of the heart s diaphragmatic surface AM HEART J 57 263 1959
38 Cabrera E and Monroy J R Systolic and diastolic loading of the heart Part II Electrocardiographic data AM HEART J 43 669 1952
39 Cabrera E and Gaxiola A A critical re evaluation of systolic and diastolic overloading patterns Prog Cardiovas Dis 2 219 1959
40 Lamb L E Grosgurin J R and Duchosal P W Vectorcardiographic studies of ventricular hypertrophy Cardiologia 28 65 1956
41 Cabrera E Gaxiola A and Eisenberg P El vectocardiograma en los crecimientos ventriculares derechos tipo sobrecarga sistolica Arch Inst cardiol Mexico 28 469 1958
42 Duchosal P W and Grosgurin J R Atlas d électrocardiographie et de vectocardiographie Basle and New York 1959 S Karger
43 Penaloza D Tranchesi J Marsico F Limon Lason R and Sodi Pallares D Vectorial analysis of the electrocardiogram in right ventricular hypertrophy I Congenital heart disease with pure or associated pulmonary stenosis Second Congress of S I B I C Acapulco Mexico April 1954
44 Sodi Pallares D and Marsico F The importance of electrocardiographic patterns in congenital heart disease AM HEART J 49 202 1955
45 Portillo B and Sodi Pallares D Semiologia electrocardiografica de la hipertrofia ventricular y sobrecarga sistólica del ventriculo derecho en los padecimientos congénitos del corazón Principia Cardiologica 6 231 1959
46 Gordon A and Goldberg H Correlation of the electrocardiographic pattern of right heart strain and evidence of right ventricular hypertension in congenital heart disease AM HEART J 42 226 1951
47 Houssay H E J and Dexter L Physiological factors involved in the production of right ventricular hypertrophy Paper presented at the IV Interamerican Congress of Cardiology Buenos Aires 1952
48 Cosby R S Levinson D C Dimitroff S P Oblath R W Herman L M and Griffith G C The electrocardiogram in congenital heart disease and mitral stenosis AM HEART J 46 670 1953
49 Johnson J B Ferrer M I and Cournand A The relation between electrocardiographic evidence of right ventricular hypertrophy and pulmonary arterial pressure in patients with chronic pulmonary disease Circulation 1 536 1950
50 Scott R C Kaplan S Fowler N O Helm R A Wescot R N Walker I C and Stiles W T The electrocardiographic pattern of right ventricular hypertrophy chronic cor pulmonale Circulation 11 927 1955
51 Torner Soler M Balaguer Vintro I and Gibert Queraltó G Elevated right ventricular pressure Its relation to the pattern of right ventricular hypertrophy AM HEART J 49:538 1955
52 Peñaloza D et al Unpublished observations
53 Blount S G McCord M C Mueller H and Swan H Isolated valvular pulmonic stenosis Clinical and physiologic response to open valvuloplasty Circulation 10 161 1954
54 Landtman B Postoperative changes in the electrocardiogram in congenital heart disease I Pure pulmonic stenosis Circulation 10 859 1954
55 Walker W J Mattingly T W Pollock B E Carmichael D B Inmon T W and Forrester R H Electrocardiographic and hemodynamic correlation in atrial septal defect Circulation 12 786 1955
56 Kahn M Bleifer S B Grishman A and Donoso E The vectorcardiogram and electrocardiogram before and after valvulotomy for pulmonic stenosis AM HEART J 58 377 1959
57 Beregovich J Bleifer S Donoso E and Grishman A Vectorcardiographic and electrocardiographic changes following surgical correction of atrial septal defect AM HEART J 59 329 1960
58 Lasser R P and Grishman A Spatial vectorcardiography right bundle branch block VIII AM HEART J 42 513 1951
59 Cabrera E Garcia Font R Gaxiola A and Pileggi F The vectorcardiogram of ventricular activation in chronic coronary heart disease AM HEART J 55 557 1958
60 Peñaloza D Gamboa R and Sime F Experimental right bundle branch block in the human heart Electrocardiographic and vectorcardiographic observations in the heart without hypertrophy Presented at the International Symposium on Atherosclerosis and

Coronary Heart Disease Mexico D F September 1959

61 Penaloza D Gamboa R and Sime F Experimental right bundle branch block in the human heart Electrocardiographic and vectorcardiographic observations in the heart with right ventricular hypertrophy Presented to the Symposium on Electrocardiography Sixth Interamerican Congress of Cardiology Rio de Janeiro August, 1960

62 Miquel C Sodi Pallares D Cisneros F *Pileggi F Medrano G A and Bisteni A* Right bundle branch block and right ventricular hypertrophy Am J Cardiol 1 57 1958

63 Del Rio R Medrano G R bio V Perez Olea J Soni J and Sodi Pallares D Right bundle branch block with right ventricular hypertrophy Am J Cardiol 4 794 1959

64 Ziegler R F The importance of positive T waves in the right precordial electrocardiogram during the first year of life Am Heart J 52 533 1956

65 Marnco F Cardenas M Pileggi F and Sodi Pallares D La onda T positiva en V1 como signo de hipertrofia ventricular derecha del nino Arch I t cardiol Mexico 27 323 1957

66 Penaloza D and Echevarría M Electrocardiographic observations on ten subjects at sea level and during one year of residence at high altitudes Am Heart J 56 811 1958

67 Penaloza D Echevarría M Marticorena E and Gamboa R Early electrocardiographic *changes produced by ascending to high altitudes* Am Heart J 56 493 1958

68 Campos J and Iglesias B Observaciones anátomo-patologicas en 49 personas normales nativas y residentes en la altura (3 00 5 000 mts) muertas en accidente Rev latinoam anat patol 1 109 1957

69 Arias J Saldana M Penaloza D and Gamboa R Unpublished observations

Case reports

Endocardial fibroelastosis in one of monozygotic twins

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Disparity in the cardiac status of monozygotic twins has been reported in the past with a different lesion being present in the two instances The present report concerns a third lesion observed in one of identical twins Fortunately the babies under discussion were closely observed shortly after birth and the details of their physical appearance carefully noted The placental structure was also described in detail The importance of this data became evident when the ravages of a disease process resulted in a loss of the close resemblance

Dr James Hawk who delivered the infants wrote as follows It was known that this patient was larger than average for the estimated gestation however I had not been able to hear two fetal hearts even though I suspected a multiple pregnancy The patient refused to have an x ray made Labor occurred two weeks early and both babies reacted well the first one being somewhat smaller than the second The mother was Rh negative so cord blood from each infant was sent to the laboratory Examination of the placentas revealed that they were fused and that there was only one chorion but two amnions and that portions of the membranes separating the babies were very thin and seemed to be in only two layers

Baby A weighed 4 pounds and 2 ounces and Baby B weighed exactly 1 pound more (5 pounds and 2 ounces) Examination of the two infants was entirely negative and they appeared to be identical The blood groups were found to be the same blood group A Rh subtypes C D and E negative The anti M anti N c and d were positive The Coombs test was negative in both instances and routine blood counts were within normal limit The smaller infant gained well and was dismissed at the age of 3 weeks at which time his weight was 5 pounds and 9 ounces He was said to have weighed 8 pounds at the age of 6 weeks

The infants were not observed again until Nov 19 1959 at which time (age 16 months) there was striking difference in the appearance of the twins Twin A weighed $19\frac{1}{4}$ pounds and was 30 inches long Air hunger was evident with a grunt on expiration retraction of the intercostal spaces and episternal notch on inspiration and an ashen gray color of the skin There was no clubbing of the fingers or toes The heart was enlarged in all diameters and there was a thrill particularly marked at the apex The rhythm was regular but the rate was quite consistently 160 per minute A generalized harsh systolic murmur was most prominent at the mitral area The rapid rate precluded definition of gallop rhythm The breath sounds were subdued over the bases of the lungs and showers of fine moist rales could be heard Hepatosplenomegaly was not present and there was no peripheral edema

Twin A was said to have never thrived as well as his sibling Pallor had been present since the age of 4 months Four days prior to this examination he had become anorexic and had developed an expiratory grunt which was quite progressive in nature Cough had been moderate but restlessness and irritability had been severe

Twin B at this time weighed $22\frac{1}{2}$ pounds and was $31\frac{1}{2}$ inches in length He showed no defect except for intense pallor of the skin and mucous membranes His hemoglobin was found to be 7 8 Gm per hundred cubic centimeters of blood

Twin A was hospitalized on Nov 13 1959 The hemoglobin was 7 Gm (hematocrit 29) the leukocyte count was 8 900 with normal differential

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Fig 1 Radiograms of the chests of the twins showing marked enlargement of the heart
Left Twin A *Right* Twin B

Fig 2 Electrocardiograms of the children *Left* Twin A The P waves are ... broad in Leads II ... There ... marked clockwise rotation in the ... the left ventricular leads suggest right ventricular hypertrophy The ... rence of ... normal left precordial pattern in the ECG of the unaffected ...

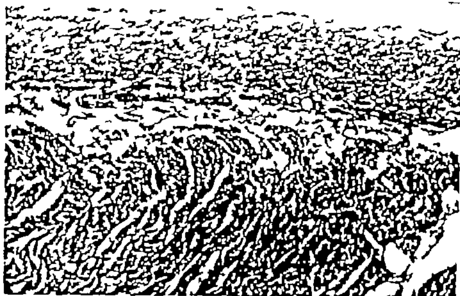


Fig 3 The endocardial layer shows marked thickening (magnification ×120 reduced ⅓)

The urine was negative The chest x-ray film showed generalized cardiac enlargement with changes at the lung bases indicative of pneumonitis or passive congestion due to cardiac decompensation

Treatment consisted of Croupette with 6 liters of oxygen per minute and tetracycline one teaspoon every 6 hours The congestive pulmonary findings had regressed by the fifth day and 175 c c of whole blood was given by slow intravenous drip This was repeated 48 hours later after which the hemoglobin level was 1? Gm per hundred cubic centimeters of blood

Definite diagnosis as to the nature of the cardiac disorder was not made and the child was discharged on Nov 20 1959 Readmission became necessary on Jan 7 1960 A moderate degree of pallor was present and the hemoglobin was found to be 11 5 Gm The cardiac findings were those of progressive enlargement of the heart The carbon-dioxide combining power was 17 mEq /L and the fasting blood sugar was 104 mg per cent Fluoroscopic examination of the chest showed the heart to be enlarged to ofold since the previous observation and the left atrium was strikingly prominent Endocardial fibroelastosis was suspected

Oxygen therapy was necessary and digitoxin 0 6 mg was given initially followed by 0 06 mg daily Forty five milligrams of chlorothiazide was given orally twice daily

The child was given the above mentioned medication at home but did not do well and was readmitted to the Community Hospital on Feb 20 1960 His weight had dropped to 17¼ pounds and the congestive failure was extreme Symptomatic care was unavailing and the patient died on March 18 1960 Necropsy was limited to the heart

Necropsy findings The heart was markedly enlarged with the apex lying in the left mid axillary line There was an increased amount of pericardial fluid and the pericardium was smooth and glistening All cardiac chambers were dilated with an increase in thickness of the musculature The myocardium was firm and reddish brown The endocardium over the left ventricle particularly along the interventricular septum was thickened and grayish white The underlying myocardium could not be seen through the endocardium in many areas The leaflets of the mitral valve were thickened with leaflets of other valves which showed no abnormal change The ductus arteriosus was closed

Multiple sections from the heart showed moderate thickening of the endocardium This is consistent with subendocardial fibroelastosis

Comment

A pathologically proved instance of fibroelastosis of the endocardium in one of monozygotic twins is presented A search of the literature fails to reveal another such report although Kempton[3] reported such a situation based upon clinical data The P wave changes found are usually not noted in the electrocardiogram of patients with endocardial fibroelastosis yet must reflect the nonspecific factor of auricular enlargement Low voltage and conduction disturbances are unusual but the conduction disturbance has been reported[4] in one infant The early onset of the disease suggests a congenital origin of it yet the occurrence in one of

Dr Ray Schw?r per?ormed th? autopsy

monozygotic twins (and an isolated instance in one family) gives no information as to any genetic factor in its origin The surviving twin will be observed closely since it is possible that he may show evidence of the disorder with the passage of time

The photographic work was done by Mr Robert Albright Indianapolis Ind

REFERENCES

1 Stadler H E Disparity the cardiac status of monozygotic twins J Pediat 4 353 19 5
2 Stadler H E and Chromiak W Discordant monozygotic twins J Pediat 49 450 1956
3 Kempton J J Endocardial fibroelastosis in one of 3 year-old twins Review 6 years later Proc Roy Soc Med 52 643 1959
4 Stadler H E Reid C A and Friedman H I Prenatal fibroelastosis (fetal endocarditis) manifested clinically by total heart block, J Pediat 36 370 1950

Traumatic aortico–right atrial fistula
Report of a case corrected by operation

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Acquired fistulous communications between the aorta and right chambers of the heart are uncommon. The majority occur spontaneously at the level of the sinuses of Valsalva which have undergone aneurysmal dilatation and ruptured into the atrium, ventricle, or pulmonary artery. Traumatic communications very rarely permit a sufficient period of survival for the observation of hemodynamic sequelae and for appropriate treatment. It is for *these reasons that the following case is* presented.

Case report

W. B., a 30-year-old male Bantu, was admitted elsewhere on May 22, 1959, after having been stabbed through the third intercostal space to the right of the sternum some hours previously. His general condition was satisfactory, and an x-ray film of his chest showed a small amount of air and fluid in the right hemithorax. On May 26, he became acutely dyspneic, but improved after the aspiration of 800 ml. of altered blood from the right hemithorax. The following day he went into shock quite suddenly, his blood pressure was unrecordable, and because further bleeding was suspected, a thoracotomy was performed. A severed right internal mammary artery was transfixed and tied, 3 pints of blood were removed from the right pleural cavity, and a 1-cm. cut was identified in the anterior aspect of the pericardium overlying the right atrium. The pericardial sac was opened and a small amount of blood was aspirated, whereupon a linear wound 1 cm. in length adjacent to and parallel with the atrioventricular groove was found to be bleeding profusely. A coarse systolic thrill over the right atrium suggested intracardiac pathology, but in the absence of suitable facilities a cardiotomy could not be performed. The atrial stab wound was closed with 2-0 silk sutures.

Some hours later, pulsatile distention of his neck veins and a loud left parasternal systolic murmur were noticed. Digoxin and [illegible] were given, with some resultant improvement, although the venous distention and murmurs persisted. On June 9, he was seen at the Cardiac Clinic, Groote Schuur Hospital. The striking signs now were grossly distended jugular veins and enlargement of the liver to 8 cm. below the costal margin; both veins and liver showed marked expansile systolic pulsation. No edema or dyspnea were noted, and the pulse appeared to be normal, having no collapsing tendency. The blood pressure was 1?0/?0 mm. Hg. The mediastinum and cardiac apex were displaced toward the left. To the right of the sternum a loud fistulous murmur could be heard enveloping the second sound, whereas a pansystolic murmur followed by a loud early diastolic filling sound were present in the third and fourth left intercostal spaces (Fig. 1). The rest of the examination was not contributory.

The chest radiograph (Fig. 2,A) showed a large collection of fluid in the right hemithorax and considerable cardiac enlargement. Left lung appeared normal; no evidence of vascular engorgement.

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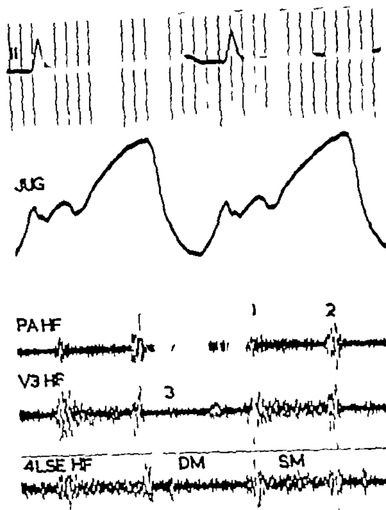


Fig 1 Preoperative phonocardiogram with accompanying jugular venous pulse tracing *HF* High frequency *PA* Pulmonary artery *V3* V3 position on anterior chest wall *4LSE* Fourth intercostal space left sternal edge (not recorded synchronously) The continuous murmur is best shown in the *4LSE* tracing third sound is seen at the *V3* position and an atrial systolic murmur at *V3* and *PA* The jugular tracing shows the partially fused CV wave suggestive of severe cuspid incompetence

The electrocardiogram showed sinus rhythm P R interval of 0 18 second vertical axis (circa 85) and widespread T inversion which was more pronounced in the right precordial lead but no evidence of right ventricular strain (Fig 3,A)

Cardiac catheterization was performed on July 1 1959 The samples of blood showed a 4 2 L min left-to-right shunt at the right atrial level (see Table I) Pressure tracings recorded from the right atrium showed a very pronounced Y descent followed by a steep presystolic A wave restriction of the X descent and partially fused C and V waves (Fig 4,A) This configuration suggested reflux into the right atrium during ventricular systole Elevation of the end-diastolic pressure in the right ventricle was in keeping with failure of this chamber (Fig 4 B)

A preoperative diagnosis communication between the was made An additional tricuspid valve as signs of tricuspid appreciated that the by an aortico right a

An operation on July 13 was a through the bed of was much enlarged be palpated over aorta was crossed opened to between the

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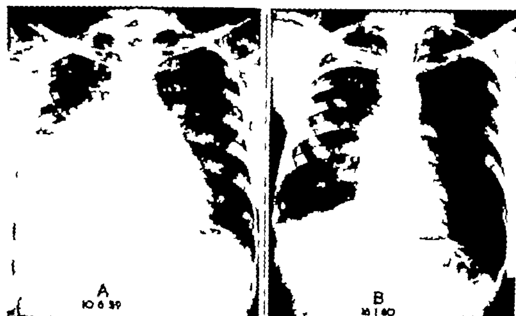


Fig 2 A Preoperative chest radiograph showing right pleural effusion and cardiac enlargement B Postoperative radiograph showing restoration of normal cardiac silhouette

With intermittent aortic occlusion the fistula was closed by means of interrupted 3 O mattress sutures which were subsequently tied over an Ivalon pledget thus sealing the breach secured. The atrium was then closed with 3 O silk sutures. The total period of perfusion was 39 min ten. Sinus rhythm with occasional ectopic beats had persisted throughout the procedure and the electroencephalogram remained normal. The patient recovery following the operation was dramatic, a striking feature the almost immediate disappearance of all signs of tricuspid incompetence and rapid return of the liver to normal.

Clinical support for complete closure of the defect was inferred from the absence of any residual murmurs or signs of tricuspid incompetence. The patient left the hospital on the patient's second postoperative day and soon returned to work. Six months later no abnormal signs were elicited; the chest radiograph was normal (Fig 2 B). The electrocardiogram showed increased voltage and slight slurring of the terminal QRS complex (Fig 3 B) probably normal variant.

Comment

Acquired communications between the aorta and right sided heart chambers constitute a grave threat to cardiac function; the duration of life depends on the size and site of the shunt. Our knowledge of the natural history of this sequence of events is derived largely from descriptions of cases of rupture of the sinuses of Valsalva. Aneurysms at this site are most frequently due to congenital weakness but may also be the result of acquired pathology such as syphilitic or mycotic aortitis. Uncomplicated aneurysms are not attended by signs or symptoms in the great majority of cases[2,3]. However their rupture is accompanied by a distinctive clinical constellation which was fully described by Thurnam in 1840 and more recently by Maud Abbott[4] in 1919 and which frequently permits the timing of this event to be accurately established. This analysis of 37 cases of ruptured sinuses reported in the literature up to

Table I Cardiac catheterization

Site	Pressure (mm Hg)	Oxygen saturation (%)
High SVC		44
Low SVC		48
High RA	15 2 (Mean 10 5)	73
Mid RA		79
Orifice of IVC		68
RV	30 0 10	75
MPA	22 14	76
RBA	100 62	93

Systemic flow 6 7 L /min
Pulmonary flow 10 9 L /min
Left to right shunt 4 2 L /min
Pulmonary vascular resistance 1 4 units

1957 indicated a mean survival time of 3.9 years following rupture. If 2 patients who lived for 10 and 15 years are excluded this mean drops to 1 year[6]: death in the majority of cases was due to cardiac failure, and in a minority to bacterial endocarditis. The chamber into which a sinus ruptures has some bearing on the symptomatology. A defect between the aorta and pulmonary artery simulates an acute form of patent ductus arteriosus, and because the lungs and left heart are immediately involved, severe symptoms generally ensue and lead to death within days or weeks. Rupture of the aorta into the right ventricle has similar effects, but provided that other vital structures such as junctional tissue and coronary vessels remain intact, the outlook improves when the break occurs more proximally between the aorta and the right atrium or superior vena cava.[7] The latter two structures dilate and thus partially dissipate the kinetic energy and volume effect of an influx of arterialized blood under high pressure, thereby relieving the strain on the pulmonary circuit and left heart. However, signs of systemic venous engorgement may then be more pronounced, as in our patient, and the systolic influx of blood into the right atrium may produce haemodynamic signs very similar to those of tricuspid incompetence. Rupture of the root of the aorta into the right ventricle with resultant right ventricular failure and functional tricuspid incompetence may produce clinical signs indistinguishable from those of aortico-right atrial fistula, and since some arterialization may then be encountered at the atrial level, cardiac catheterization may also be misleading. The tricuspid valve may itself

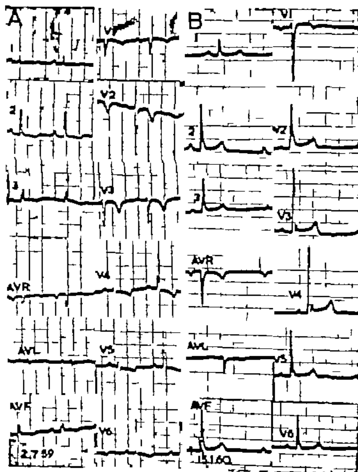


Fig. 3. A. Preoperative ECG showing widespread T inversion. *B.* Postoperative ECG showing return to normal.

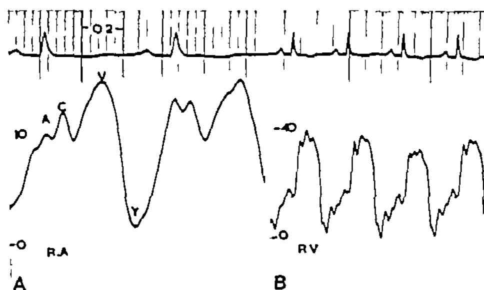


Fig 4 A Right atrial pressure tracing The large systolic w ve composed of partall fused A C and V waves suggests tricuspid incompetence B Right entricular pressure tracing The elevated end diastolic pressure suggests a failing chamber

be deformed by the aneurysm or damaged in traumatic cases with resultant tricuspid incompetence

Thus three possible mechanisms may be associated with the dynamic changes of tricuspid incompetence and the methods described above are clearly inadequate to distinguish which is operative in a given case The fistulous murmur is likely to obscure any possibly associated murmur of tricuspid incompetence and the dynamic effects of tricuspid incompetence as reflected in the jugular veins and right atrial pressure tracings may be closely simulated by a leak from the aorta into the right atrium When indicated the use of dye dilution and cineangiocardiographic techniques may provide the answer although final diagnosis may usually be deferred until atriotomy Correction by operation is clearly indicated whenever possible in view of the grave prognosis of untreated cases and reports of successful repair are appearing with increasing frequency [8,10]

The foregoing observations can only infrequently be related to cases of traumatic aortico right heart fistulas Such lesions are generally rapidly fatal but occasionally as in our case a prompt operation may remove the danger associated with the external heart wound while leaving an intracardiac shunt which can later be dealt with in definitive fashion A few reports of repaired traumatic aortico right ventricular fistulas have already appeared [11,12] In the available literature no other example of successful surgical repair of traumatic aortico right atrial fistula could be found

Conclusions

A case of traumatic aortico right atrial fistula caused by a stab wound in the chest is described Right heart failure rapidly developed and promptly regressed following successful open heart closure of the defect

We wish to thank Dr A Landau and Dr R Hewitson for referring the case for study and treatment and the Superintendent Dr J Burger for permission to publish We should also like to acknowledge the assistance received from our technicians M L W Piller and M S Joseph

REFERENCES

1 Barnard C N Phillip W L deVilliers D R Casserley R D Hewitson R P van der Riet R L and McKenzie M B Some experiences with intracardiac surgery using the helix reservoir bubble oxygenator with total cardiopulmonary bypass South African M J 33 789 1959
2 Jones A M and Langley F A Aortic sinus aneurysms Brit Heart J 11 325 1949
3 Oram S and East T Rupture of aneurysm of aortic sinus (of Valsalva) into the right

side of the heart Brit Heart J 17:541 1955
4 Thurnam J Med Chir Trans 23 323 1840 Cited by Oram and East
5 Abbott M E Contributions to medical and biological research Sir William Osler Memorial P B Hoeber 2 899 1919 Cited by Sawyers Adams and Scott
6 Sawyers J H Adams J F and Scott H W Surgical treatment for aneurysms of the aortic sinuses with aortico atrial fistula Surgery 41 26 1957
7 Herrmann G R and Schofield N D The syndrome of rupture of aortic root or sinus of Valsalva into the right atrium Am Heart J 34 87 1947
8 Morrow A B Baker R B Hanson H E and Mattingly T W Successful surgical repair of ruptured aneurysm of the sinus of valsal Circulation 16:533 19 7
9 Kay J H Anderson R M Lewis R L and Reinberg M Successful repair of sinus of Valsalva left atrial fistula Circulation 20 427 1959
10 Lillehei W B Stanley P and Varco R Surgical treatment of ruptured aneurysms of the sinus of Valsalva Ann Surg 116 459 1957
11 Smyth N P D Adkins P D Keiser G A and Catalayud J Traumatic aortic right ventricular fistula Surg Gynec & Obst 109:566 1959
12 King H and Shumacker H B Surgical repair of a traumatic aortic right ventricular fistula J Thoracic Surg 35 734 1958
13 Morris G C Foster R P Dunn J R and Cooley N M Traumatic aortico- entricular fistula report of two cases successfully treated Am Surgeon 24 883 1958 Cited by Smyth et al

Clinical pathologic conference

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Clinical review

First Admission (April 7 1959 to April 10 1959) This -year-old white boy was admitted to Presbyterian St. Luke Hospital on April 1959 with history of a known heart murmur and precordial bulge since birth. The heart murmur was discovered immediately following normal delivery there was not then nor had there ever been cyanosis. He had always been active and there was no limitation of activity although his mother noticed some dyspnea on strenuous exertion, such as running up flight of stairs. There was no history of squatting orthopnea, ankle edema, syncope hypertension or chest pain.

PHYSICAL EXAMINATION The blood pressure was 110 68 mm. Hg in the left arm and 114 72 m the right arm The pulse was 84 per minute and regular The child appeared to be within the lower limits of development for the stated age The tonsil were enlarged but not inflamed. The lungs were clear There was a marked precordial bulge. The cardiac apex was in the anterior axillary line t about the fifth or sixth left intercostal space On auscultation the first heart sound at the apex was loud. The second heart sound was not audible t the apex. At the base the first heart sound was not audible. The second heart sound was loud and highly split and more prominent to the left of the sternum. There was a very loud crescendo-decrescendo systolic murmur occupying the entire systolic phase audible throughout the precordium but loudest in the second and third left intercostal spaces. In the same area there was loud rumbling diastolic murmur decrescendo in character The peripheral pulses, including the femoral were bilaterally strong and regular There was no clubbing venous distention or edema.

LABORATORY DATA The hematocrit was 40 hemoglobin, 13 6 Gm per cent white blood cell count, 6 450 showing 42 per cent lymphocytes, 54 per cent neutrophils 4 per cent band per cent monocytes The urinalysis was normal The Hanger test was negative thymol turbidity was 3 9 units. The serology was negative. The electrocardiogram was interpreted as showing right heart strain and suggesting right ventricular hypertrophy Cardiac fluoroscopy and chest ray films showed cardiac enlargement, probably right ventricular There was vigorous pulsation of the enlarged pulmonary arteries which was greater on the left The right pulmonary artery appeared much less enlarged. The lungs were undervascularized There was difficulty in entering the pulmonary artery on cardiac catheterization. The results of catheterization are shown in Table I

Second Admission (May 7 1959 to May 13 1959) The patient was readmitted on May 7 1959 for further study and treatment

PHYSICAL EXAMINATION The blood pressures (mm Hg) were right arm 115/70 left arm 11 /80

Table I Catheterization findings

Position of the catheter	Oxygen content (vol %)	Pressure (mm Hg)
Superior vena cava	12 65	2 0
Upper right atrium	12 64	2/0
Middle right atrium	12 13	2 0
Lower right atrium	1 11	
Inferior vena cava	10 15	
Right ventricle inflow tract	13 01	/0
Right ventricle outflow tract	13 50	5 0
Main pulmonary artery	12 9	25/8
Left pulmonary artery	13 06	25/8
Right pulmonary artery	13 15	25/8
Femoral artery	15 92	70 50
Capacity	16 72	
Saturation	95 2%	

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right leg 1 8/80. The pulse was 100 and regular. The chest was clear. Forceful Grade 4 systolic and Grade 2 diastolic thrills were present over the entire precordium, particularly at the left sternal border at the fourth intercostal space. The systolic thrill was present in the neck. There was a Grade 5 harsh systolic murmur at the left sternal border in the fourth intercostal space which was transmitted to the back, entire chest below the diaphragm, neck, and arms to the elbow. A loud diastolic murmur was heard over the same area and transmitted to the entire precordium and between the scapulae. This diastolic murmur was rough and not blowing. There was no edema, cyanosis, or unusual peripheral vascular findings.

LABORATORY DATA. The hemoglobin was 12.7 Gm. per cent, white blood cell count 6,400, showing 73 per cent neutrophils, 2 per cent bands, 24 per cent lymphocytes, and 1 per cent eosinophil. The urinalysis was negative. A chest x-ray film showed the heart to be enlarged to the left, and there was marked increase in the size of the pulmonary arteries. There was an increase in the vascularity of the lung with the exception of the right lower lobe. A venous angiogram demonstrated a large right ventricle and large pulmonary arteries. There was blanching of the right ventricular contrast by shunt. No infundibular or pulmonary valvular stenosis was identified. The aorta was small and dextroposed and displaced anteriorly. An electrocardiogram was thought to be compatible with right ventricular hypertrophy, possibly combined with left ventricular hypertrophy, with right ventricular hypertrophy predominant.

HOSPITAL COURSE. On May 12 the patient underwent reparative operation with cardiopulmonary bypass. Postoperatively, the patient bled considerably and went into shock, necessitating several transfusions. He was reopened but no actual point of bleeding could be found. Numerous oozing points were stopped and the chest was closed again. After that episode the patient went into cardiac arrest about 1 hours after the second operation. The chest was opened, the heart massaged, and with supportive therapy the heart was brought back to normal sinus rhythm. About a half hour after the chest was closed the patient went again into cardiac stand till and expired.

Discussion

DR. OASCL. On the basis of the history of this 7½ year old white boy, I may state that this patient had a noncyanotic type of congenital malformation of the heart. I can definitely exclude all serious forms of the cyanotic types of congenital malformation with the following exceptions: mild clinically noncyanotic type of tetralogy of Fallot, anomalous entrance of all pulmonary veins into the supracardiac area with an atrial septal defect, truncus communis with large pulmonary arteries, and mild forms of anatomic Eisenmenger complex. Although patients with the conditions just mentioned almost always reveal some peripheral arterial oxygen unsaturation, they may appear clinically as belonging to the noncyanotic type. The arterial oxygen unsaturation is often not recognized clinically until it is below 80 per cent or even lower.

On the basis of the physical examination and conventional laboratory tests we can state the following: the heart is definitely enlarged; it is in the fifth or sixth left intercostal space in the anterior axillary line and the presence of a precordial bulge usually signifies right ventricular hypertrophy; the normal femoral pulses and the normal blood pressures exclude a coarctation of the aorta; the very loud pansystolic murmur maximal at the second and third left intercostal spaces signifies the presence of a ventricular septal defect. This murmur obliterates the first heart sound at the base and the second heart sound at the apex. This proves that the murmur is pansystolic and differentiates it from a loud ejection systolic murmur due to pulmonary and/or aortic valvular stenosis, because the latter starts after the first heart sound and ends before the closure of the involved valve. The second heart sound at the base is reported to be loud and slightly split. It is of the utmost importance to analyze this second sound. Does the slightly split mean a single sound or that the second component (the pulmonic closure) of the second sound is diminished in intensity?

In tetralogy of Fallot the second sound at the base is usually single and loud because only the closure of the aortic valve is heard at this area. There usually is no splitting of the second sound at the pulmonary area because an insufficient amount of blood enters the pulmonary vessels under the lower than normal pressure. In mild cases of tetralogy of Fallot one may hear the closure of the pulmonary valve because the stenosis is not marked and a greater amount of blood enters the pulmonary artery. But even in these mild cases the pulmonary component of the second sound is diminished in intensity and is delayed. Therefore the statement in the protocol that the second sound is loud and lightly split most probably means that it was single. It was certainly not delayed.

We can exclude the presence of valvular pulmonary stenosis with a normal



Fig 1 Posteroanterior chest radiograph showing large pulmonary arteries moderately enlarged heart and translucent right lower lobe

root i e isolated pulmonary stenosis because of the pansystolic murmur and a single loud second sound at the pulmonary area In isolated pulmonary stenosis one hears an ejection type of systolic murmur which begins after the first heart sound and ends before the closure of the pulmonic component of the second sound This pulmonic component is always delayed and diminished in intensity so that one therefore hears a weak second sound In the vast majority of all these patients a high frequency systolic click is heard following the first heart sound and we believe that this early systolic click is a result of the opening of the stenosed and thickened pulmonary valve Its pathogenesis is similar to the opening snap of the stenosed mitral valve that one hears in mitral stenosis In extremely severe cases of isolated pulmonary stenosis with practically no movement of these cusps this early click is as would be expected not heard In some of these patients the pulmonary component of the second sound also cannot be heard although the phonocardiogram will usually show this markedly delayed and low intensity pulmonic closure However these patients with severe isolated pulmonary stenosis still have an ejection type of systolic murmur and they are usually definitely cyanotic either because of a right to left shunt at the atrial level (through the foramen ovale or atrial septal defect) or because of a marked increase in peripheral arteriovenous oxygen difference

The presence of a loud rumbling diastolic murmur in the second and third left intercostal spaces presents a real diagnostic problem because one does not hear this murmur in either tetralogies or in isolated pulmonary stenosis I shall comment on this later

Examination of the roentgenograms (Figs 1 and 2) reveals enlargement of the right ventricle and no enlargement of the left atrium and the pulmonary arteries especially the left one are markedly enlarged and pulsate vigorously on fluoroscopic examination The lungs particularly on the right side are undervascularized

I would now like to see these roentgenograms and to hear Dr Buenger's interpretation

DR BUENGER The significant findings in the angiocardiogram (Fig 3) are confined



Fig. Lateral chest radiograph showing marked right ventricular hypertrophy and absence of left atrial enlargement

to the right side of the heart There is a blanching of the outflow tract due to a left to right shunt Because of this the size of the infundibulum is not discerned but the area just below the pulmonary valve does not appear to be stenosed The pulmonary valve cusps are never visualized There is no valvular stenosis The main pulmonary artery is very large as is the left main branch The right pulmonary artery is large but not markedly so There is a very striking lack of vascularization of the right lower lobe but the pulmonary artery trunks leading to it appear no smaller than those leading to the other lobes of both lungs This suggests a localized vascular stenosis or marked lobular emphysema The rest of the lung appears to have normal vascularity

DR GASUL The electrocardiogram which I am now examining reveals a right axis deviation The R in Lead aVR measures 8 mm and the R in Lead V_1 is 10 mm There is a definite S wave present in Lead V_1 This is an adaptation type of right ventricular hypertrophy and it signifies that the pressure in the right ventricle is not higher than that in the left ventricle If the pressure in the right ventricle is higher than that in the left ventricle as occurs in severe isolated pulmonary stenosis the electrocardiogram often shows the barrage or systolic overfilling type of right ventricular hypertrophy I like the term adaptation type of right ventricular hypertrophy because this clearly defines that in the presence of an associated ventricular septal defect the right ventricle adapts itself to the pulmonary stenosis and sends some blood through the hole in the septum into the aorta In severe isolated pulmonary stenosis the right ventricle has no other outlet and must empty its contents through the stenosed area only into the pulmonary circulation

Cardiac catheterization confirms the presence of a right to left shunt at the ventricular level and the presence of pulmonary stenosis The report does not state whether there was infundibular and/or valvular stenosis present The pressure in the right ventricle is 75/0 mm Hg and in the pulmonary artery 25/8 mm Hg The pressure in the femoral artery is noted to be



Fig 5 Left ventricular view showing defect of ventricular septum

lot is quite different than in cases of pulmonary stenosis

DR TRUEHEART The heart was enlarged This was due mostly to a tremendous hypertrophy and dilatation of the right ventricle (Fig 4) The crista had been surgically altered It was therefore difficult to tell how much stenosis of the infundibulum there had been The pulmonary orifice was somewhat smaller than normal There was no pulmonic valve In its place there was a low rim of valve like tissue In the right ventricle beneath this rim there was another band of thick fibroelastic tissue which thus aided in the formation of a separate small infundibular chamber The pulmonary trunk and the right and left pulmonary arteries were markedly dilated up to the hili of the lungs and the wall of the pulmonary trunk was thickened The secondary branches of both pulmonary arteries were relatively small as compared to the arteries themselves but it could not be stated that they were smaller than normal

The left ventricle was normal in size and thickness The ventricular septum at its base presented a defect which measured about 1 5 cm in greatest dimension (Fig 5) This was covered by a Teflon patch but a residual defect remained The aorta straddled the interventricular septum emerging from both ventricles The various points of surgical intervention related to the cardiopulmonary bypass showed no abnormality There was 500 c c of bloody fluid in each side of the chest cavity The anterior portions of the right upper and lower lobes showed small infarcts In addition microscopically both lungs showed severe pulmonary edema and hemorrhage accompanied by inflammatory cells

In summary then the clinical diagnosis made by Dr Gasul is borne out by the pathologic findings We are dealing with tetralogy of Fallot with absence of the pulmonary valve This syndrome and pathologic complex were recently described by Miller White and Lev [1] We do not know the anatomic base of the lack of vascularization of the right lower lobe

Diagnosis Acyanotic tetralogy of Fallot with absence of the pulmonary valve

REFERENCE

1 Miller R A White H and Lev M Congenital absence of the pulmonary valve clinical and pathologic syndrome Circulation 18:749 1958

Annotations

Notes on cardiovascular disease in Africa

As encountered by an American physician on a brief visit to that continent in March and April, 1959

A cardiological tour of several countries in Africa in the spring a year ago was of such great interest to me and quite possibly to others that I am submitting this brief account to the Journal.

Invited by the students of the University of Cape Town to spend three weeks there and one week at the Witwatersrand Medical School in Johannesburg, I traversed the length of Africa on the east, stopping in Cairo, Egypt, in Nairobi, Kenya, and in Kampala, Uganda, to visit the hospitals and medical schools in order to determine the amount of cardiovascular disease in those places. On the way home from Johannesburg I stopped in Leopoldville in the Belgian Congo and in Brazzaville and Lambaréné (the location of Dr. Schweitzer's hospital), the latter in the Republic of Gabon, formerly a part of French Equatorial Africa.

Through the kindness of many of the physicians in those cities I was given the opportunity to examine patients, to see autopsy material, and to go over hospital and statistical records in order to accumulate some idea of the frequency of the different kinds of heart disease and of cardiovascular disease as a whole in much of Africa. I did not visit the northwestern part of the continent, but I have been told that somewhat the same situation exists in the southern part as we found in the republics of the Congo and Gabon. In the northernmost part of West Africa there is apparently some similarity with the findings in Egypt.

Let me take up the various kinds of heart disease as I saw them or as I was told about them on this African visit.

Congenital heart disease I found everywhere, quite possibly in the same relative degree as we see it ourselves, although as a rule there are only crude statistics available. Patency of the ductus arteriosus, septal defects, and the tetralogy of Fallot are not at all rare, and here and there surgical correction of these lesions is being carried out, especially in South Africa.

Rheumatic heart disease is common in all the countries I visited and ranks about even with hypertensive heart disease in Egypt and in South Africa. It is somewhat less common than hypertensive heart disease in Equatorial Africa. Rheumatic fever as such is often difficult to recognize, but the valvular lesions which result from it are quite common, and a number of lesions are being corrected surgically, especially, of course, mitral stenosis.

Syphilitic cardiovascular disease is becoming rare throughout Africa, although in some less advanced areas several per cent of the cardiovascular cases are still due to syphilis.

Infestation by Schistosoma (the Bilharzia parasite) is quite common in certain areas, especially Egypt and East Africa. It is responsible in some places for a third of all the cases of hypertension and at least a few of the cases of chronic cor pulmonale.

Cor pulmonale, due to pulmonary disease and obstruction of the pulmonary circulation, is quite frequent in many of the countries. Apparently it is due largely to fibrotic changes in the lungs secondary to infection or to emphysema, but also, although much less commonly, to actual blocking of the pulmonary circulation by the Bilharzia ova.

One of the most interesting of my medical experiences was the finding of two other types of heart disease which are rare in the Western world. The most extraordinary is that which has been called by Davies of the Makerere Medical School in Kampala, Uganda, *endomyocardial fibrosis* (with or without elastosis, which as such is a different entity). Although it is rarely seen elsewhere in Africa, this condition of extensive deformity of the heart muscle, in particular by fibrosis and calcification, is quite common in East Africa among the Blacks. It ranks there about even in prevalence with rheumatic heart disease and on occasion resembles it clinically, often occurring as it does in relatively young adults. Dr. Davies showed me many examples in his collection of pathologic specimens, and I saw a few clinical cases. The cause of this fantastic disease is unknown. It has been variously attributed to infection, to malnutrition, and to other factors ill defined.

A second type of unusual heart disease that I encountered occasionally in all parts of Africa is probably somewhat like that which we see elsewhere in the world, namely, *cardiac enlargement and failure*, mostly left ventricular, *of unknown cause*, which occurs at all ages. I saw a number of such specimens and cases, especially in South Africa.

Pericarditis is common in Africa, including the

associated with rheumatic heart disease and myocardial infarction. The usual infectious factors are to blame, particularly viral and tuberculous factors. As a result of the more effective treatment of tuberculosis by antibiotics in the last few years more cases of constrictive pericarditis have been seen recently in Egypt and now are being more actively treated by pericardial resection. When tuberculosis as an infection decreases there will be less of this type of operation to perform.

Hypertensive heart disease is common everywhere and is actually, I believe, the most common of all types of heart disease throughout the continent. Why hypertension is so common is not at all clear, but it is apparently found even in the remote parts of the jungle, although much more investigation as to this matter needs to be made. This subject is of considerable interest because we have long wondered whether hypertension in the American Negro has been acquired since his arrival in the Western world. Hypertension accounts for as much as 50 per cent or even more of all cardiovascular cases in tropical West Africa. Cerebrovascular involvement does occur but much less commonly than the cardiac sequelae.

Finally, *coronary heart disease* varies extraordinarily in its prevalence in Africa. It is quite common in Egypt, especially among the well-to-do, and also in East and South Africa among the Whites and East Indian populations, but it is very rare, at least in youth and middle-aged persons, among the Blacks, especially the Bantus. In the Bantu atherosclerosis of the coronary arteries of moderate degree is found in the oldest age group, but it rarely leads to involvement of the heart, and then only at a very different age than in the Whites and East Indians. This situation is somewhat like that found in Southern Japan where the disease is most prevalent among the older age group, and in this respect there is a difference of about 25 years of age between the Southern Japanese on Kyushu at Fukuoka and the Bostonians in the U.S.A. represented at autopsy at the Massachusetts General Hospital. A comparison of the degree of coronary atherosclerosis in 350 Japanese adults with that seen in a similar number of adults at the Massachusetts General Hospital showed the same levels in the Boston population at the age of 45 years as in the Fukuoka population at the age of 70 years. The reason for this great discrepancy in the degree of coronary atherosclerosis and its effect on the heart through the complication of thrombosis is one of the prime reasons for the need to intensify international epidemiological cardiovascular research. Whether race plays a role or, more likely, whether the way of life are the cause we do not know yet for certain, but it is true that the Bantu is just beginning to emerge from his primitive way of life under the influence of which in the past he has been much undernourished and yet usually more active physically than his white neighbor. The mixed Colored population of Cape Town hold an intermediate position as to the prevalence of coronary heart disease between the extremes found among the Whites on the one hand and the Bantu on the other.

Arrhythmias, neurocirculatory asthenia, and cardiac neurosis seem to be universal throughout Africa as in other parts of the world.

In conclusion, I believe that much profitable cardiovascular epidemiological research can be done in Africa to increase our knowledge of the factors responsible for heart disease and that such research can eventually lead to protection of people throughout the world from the heart diseases still found in youth and middle age.

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*The author will be glad to refer the reader to tables of the racial incidence of different types of cardiovascular disease in Egypt, East Africa (Kenya and Uganda), Cape Town (South Africa), and Leopoldville (the Belgian Congo).

Right ventricular hypertension as a cause of precordial pain

Chest pain like that of angina pectoris due to coronary atherosclerosis is frequently encountered in young individuals who suffer from a variety of circulatory abnormalities associated with high right ventricular pressure. We have recently observed such a patient, a 19-year-old farm boy with exertional chest pain in whom a positive electrocardiographic exercise test showed 2 mm. depression of the S-T segments after standard exercise. In this patient with a typical ischemic response to exercise pulmonary hypertension was associated with a large patent ductus arteriosus. The patient died during operation, and at autopsy the coronary arteries were found to be normal. The myocardial ischemia responsible for the anginal pain was presumed to be the result of altered hemodynamics. Similar pain in the presence of normal coronary arteries has been reported in patients with pulmonary stenosis. The finding of fibrosis of the right ventricle in patients with this disease supports the conclusion that the pain originates in an ischemic right ventricle.

The right ventricular systolic pressure is normally less than the diastolic pressure in the aorta, and hence right ventricular coronary flow continues throughout systole, whereas left ventricular coro-

nary flow ceases The systolic right ventricular intracavitary pressure therefore important determinant of right ventricular coronary flow and ischemia might be anticipated in association th elevated right ventricular pressure Right ventricular hypertension cannot be the onl factor involved since right ventricular pressures of the same or greater magnitude are found in the presence of ventricular septal defects association with either pulmonary stenosis or pulmonary vascular disease yet angina pectoris does not occur

I the presence of intact intraventricular septum right ventricular pressure may exceed left ventricular pressure especially in patients with pulmonary stenosis When the septum intact the diastolic pressure the hypertensive right ventricle may be elevated and exceed the diastolic pressure in the left ventricle With large ventricular septal defect pressures in the two ventricles remain equal throughout the cardiac cycle It may be that the effect of these diastolic pressure relationships on the collateral circulation the heart explain the presence of angina pectoris only in patients with right ventricular hypertension and an intact septum

The fact that angina pectoris not universall present in association th right ventricular hypertension seems best explained by the normal variability in the anatomy of the coronary circulation The available clinical observation indicate th t the chest pain of patients with pulmonary stenosis and pulmonary hypertension the result of right ventricular myocardial ischemia secondary t reduced coronary flow It seems reasonable to explain the reduced coronary flow on the basis of the elevated right ventricular intracavitary pressure during both systole nd diastole

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REFERENCES

1 Lasser R P and Genkins G Chest pain patients th isolated pulmonic stenosis Circulation 1 59 1957
2 Gregg D E Coronary circulation in health and disease Philadelphia 1950 Lea & Febiger
3 Stuckey D Cardiac pain in association with mitral stenosis and congenital heart disease Brit Heart J 1 397 1955

Control of body fluid volume

The volume of fluid in the body is controlled within narrow limits for 0 per cent of the adult body fluid and when measured under standardized conditions total body weight varies less than ±1 per cent over long period as Fowler[1] has shown Although the stability of this volume in normal people has been recognized since the work of Henderson the mechanism by which this regulation accomplished has not been adequately explained

Variations in temperature growth and control of osmotic pressure of the body fluids influence the water content of the body If after the effects of these systems have been accounted for independent control of the volume of body water occurs then one must postulate that volume control per se exist Since Peters first discussed the concept of volume receptor many workers have examined this problem Borst[2] postulated that the vascular compartment monitored changes in fluid volume t alter cardiac filling pressure nd output changes in cardiac output cause variation in the amount of sodium and water retained Low and Sayers[3] made clinical observations on edematous patients and concluded that volume-controlling mechanism in existed with volume-disturbing and volume restoring components and that the sensitivity of this mechanism was altered in edematous states Recentl Lowe[4] has presented data collected from normal individuals and those with disturbance in their regulation of fluid storage From these observations hypothesis was elaborated The body is regarded as a storage of complex fluid in many compartments Through the vascular compartment passes continuous inflow and outflow of solvent and solute occur The fluid in this compartment monitored for osmotic pressure and changes in volume and from this information the inflow nd outflow of solvent is adjusted by means of feed back control thus achieving self regulation of the volume of the system This view is challenging but reasonable and there other ideas to support t

The osmotic pressure of the vascular compartment controlled by the intake nd excretion of water and salt Verney has shown that osmoreceptors in the hypothalamus respond t changes in tonicity of the extracellular fluid nd so regulate the secretion of antidiuretic hormone by the neurohypophysis the antidiuretic hormone ensures adequate retention of water by the renal tubules With th mechanism functioning the volume of extracellular fluid will depend on the amount of sodium present Th normall controlled by the salt retaining hormone aldosterone which is secreted by the zona glomerulosa of the adrenal cortex nd also acts upon the renal tubules

Experiments designed to show the relation between the sodium in the vascular compartment and the secretion of aldosterone support the interpretation that this is brought about by the effect of sodium on extracellular fluid volume Bartter Mills Biglieri and Delea compared changes extracellular fluid volume produced by infused water isotonic saline nd hypertonic saline load th that produced by albumin phlebotomy nd red cell reinfusion It appeared that extracellular fluid volume exerts control over the secretion of aldosterone Ordi

of the inferior vena cava above the liver increased the secretion of aldosterone. This increase was maintained after release of the constriction if the vagi in the neck were divided during the experiments but not with the vagi intact. Vagal section alone did not alter the secretion of aldosterone. Similarly it was found that constriction of the common carotid artery low in the neck produced increased secretion of aldosterone but that this did not occur if the carotid sinus was denervated beforehand. McCally, Anderson and Farrell[9] placed sutures through the atria of dogs. Whereas traction on the right atrium depressed the secretion of aldosterone within an hour, stretching the left atrium was without effect. The afferent limb to release of aldosterone, therefore, appears to depend on an unusual physiologic mechanism in that the stimulus of decreased baroceptor stimulation leads to increased production of aldosterone but removal of the stimulus alone will not reduce secretion. For this second mechanism involving the vagus nerve is required. The evidence so far suggests that the receptors lie in the right auricle or great veins although receptors at other sites may play some part. Pearce[20] found that vagotomy and denervation of the carotid sinus did not prevent the diuresis which followed expansion of the plasma volume with isotonic infusion. He concluded that additional receptors must contribute to the afferent component.

Observations on dogs by Rauschkolb[21] and Farrell[22] suggested that the secretion of aldosterone was stimulated by a hormone from the brain. Recent work by Davis[23] and Denton, Goding and Wright[24] has strengthened this view. Davis showed by cross circulation experiments that if the blood from a dog with inferior vena caval obstruction was passed through the adrenals of a normal dog the secretion of aldosterone increased, and fell again when the cross-circulation was stopped. Denton, Goding and Wright used trained conscious sheep with neck adrenal transplants for adrenal infusion and arterial cross-circulation experiments, measuring changes in salivary electrolytes but not aldosterone itself. They found that changes in the concentration of electrolytes in the blood of the adrenals may be a contributory cause of changes in electrolyte active steroid secretions occurring in sodium-deficiency but could not account for the whole range of function recorded. The cross-circulation experiments showed that there was considerable stimulus to secretion from the adrenal of electrolyte active steroid when the blood of a sodium-depleted adrenally insufficient donor animal was passed through the adrenal transplant of another animal which was in normal sodium balance. Since this stimulation did not appear to be due to corticotrophin, action by a tropic hormone appears probable. The central integration of information received from the afferent loop and the site of tropic hormone formation is unknown. Farrell[4] has recently reported that this hormone is concentrated in the region of the pineal and subcommissural body.

The raised levels of aldosterone in patients with edema and ascites make it clear that control does not depend upon total extravascular fluid volume. In these cases it can be argued as Ross[14] has suggested that there is an increase in extracellular volume but not an increase in the area of the vascular compartment which monitors volume. Any disturbance then of Starling's[27] equilibrium will permit an excessive flow of water and solutes through the capillary wall resulting in reduction of the vascular volume and stimulation of the aldosterone secreting mechanism. If this capillary leak persists hyperaldosteronism will continue to result in further retention of sodium and accumulation of fluid. In congestive cardiac failure, nephrosis and the edema of hypoproteinemia the disturbance is general and generalized edema will result when the lymphatic pathways are unable to drain the excess fluid. If the disturbance is localized as in the case of elevated intrahepatic portal pressure sequestration of fluid into the peritoneal cavity will occur. Courtice and Simmonds[28] have shown that this fluid is drained principally by the lymphatics of the diaphragm into large collecting ducts in the thorax. As this system becomes fully loaded (and its carrying capacity is large) ascitic fluid collects reducing the effective plasma volume and setting in motion the process which leads to the retention of salt and fluid.

Although many gaps remain in our knowledge of the control of body fluid volume the pattern of the regulating mechanism is emerging. Receptors monitor the volume of some portion of the vascular compartment and so activate neuronal-endocrine feed back pathway which acts on peripheral targets to produce the changes essential for keeping body fluid volume within narrow limits.

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REFERENCES

1. Fowler, R., Jr.: Control of body water content: a study of day-to-day variation in humans and rabbits, Australasian Ann. Med. 4:123, 1955.
2. Henderson, L. J.: On volume in biology, Proc. National Acad. Sc. 2:654, 1916.
3. Peters, J. P.: Body water, Springfield, Ill., 1935, Charles C Thomas.
4. Borst, J. G. G.: The maintenance of an adequate cardiac output by the regulation of the urinary excretion of water and sodium chloride; an essential factor in the genesis of edema, Acta med. scandinav. 130 (Suppl. 207), 1948.
5. Low, T. E., and Sayers, B. McA.: Control of the water content of the body, Australasian Ann. Med. 1:51, 1952.
6. Lowe, T. F.: The nature of the control of body fluid volume in man, Phys. Med. Biol. 4:126, 1959.
7. Verney, E. B.: The antidiuretic hormone and the factors which determine its release (Croonian Lectures), Proc. Roy. Soc. London B 135:25, 1947.
8. Bartter, F. C., Mills, I. H., Biglieri, E. G., and Delea, C.: Control and physiologic action of aldosterone. *In* Recent progress in hormone research, New York, 1959, Academic Press, p. 311.
9. McCally, M., Anderson, C. H., and Farrell, G. L.: The effects of atrial stretch on aldosterone secretion. Proceedings of the 40th Meeting

Endocrine Society San Francisco 1958 p 119
10 Pearce J W The effect of vagotomy and denaturation of the carotid sinus on diuresis following plasma volume expansion Canad J Biochem & Physiol 37 81 1959
11 Rauschkolb E W and Farrell G L Decreased aldosterone secretion in decapitated dogs J Clin Endocrinol 16 915 1956
12 Farrell G L Abstracts of meeting of endocrine society New York, 1957 p 32
13 Davis J O Proceedings of the Laurentian Hormone Conference 1958 In Recent progress in hormone research New York, 1959 Academic Press p 298
14 Denton D A Goding J R and Wright R O Control of adrenal secretion of electrolyte active steroids Brit M J 2 447 and 522 1959
15 Farrell G L The physiological factors which influence the secretion of aldosterone In Recent progress in hormone research New York, 19 9 Academic Press p 275
16 Ross E J Aldosterone in clinical and experimental medicine, Oxford 1959 Blackwell Ltd p 107
17 Starling E H On the absorption of fluids from the connective tissue spaces J Physiol 19 312 1896
18 Courtice F C and Simmonds W J Physiological significance of lymph drainage of the serous cavities and lungs Physiol Rev 34 419 1954

Ultrastructure of coronary vessels

The student of coronary heart disease should be not be personally conversant with a variety of techniques and disciplines depends on information obtained by the clinician statistician biochemist physiologist morbid anatomist, and histologist. The field is widening and the electron microscope is now becoming significant.

The information on detailed structure that has become available in the last few years in variety of tissues has not only been astonishing (both confirming and extending observations made at the upper limits of resolution of the light microscope) but promises thoroughly satisfactory integration of structural and functional findings Every tissue has been illuminated and its intimate secrets revealed—even if many are still not understood

New techniques require different yardsticks Here tissue fixation must be immediate—the slight delays that were apparently unimportant in ordinary histology allow serious demonstrable changes in fine cytological structure Hence at present attention must usually be directed to experimental material to the exclusion of human tissues Within this range important information is obtainable In addition to observation on muscle others have been made on the ultrastructure of the various layers of blood vessels from the aorta to the capillaries In different vessels endothelium [1,4] elastic tissue and smooth muscle[4] have all been studied

In the coronary vessels the endothelial lining is a continuous sheet, the cells overlapping at their margins Some of these send processes through the internal elastic lamina which is thus a fenestrated sheet these may be important in the transfer of material to deeper layers. The phenomenon of uptake of material by cells—the pinocytosis described by Lewis in 1931—has now been observed at a new level Other cytological detail have been noted but their significance is still speculative

Atherosclerosis induced by the feeding of cholesterol has been studied in the aorta and coronary arteries Globules of material presumably lipid were apparent overlying endothelial cells in the stage of acute lipemia some of these were porous enclosing irregularly shaped vacuoles This material appeared to be also within and beneath the endothelial cells

The internal elastic lamina showed irregular focal swelling with corresponding loss of density and of fine fibrillar structure This was deduced to be due to solid solution of lipid in the elastic tissue Changes in smooth muscle such as formation of cytoplasmic vacuoles and increase in intercellular collagenous material were also demonstrated Such appearances in presumable muscle cells may support some of the earlier views regarding the origins of foam cell Despite the conjectural nature of some of the suggestions the observations are clear-cut Human atherosclerosis may be (and in some forms undoubtedly is) different from the experimental condition described in which the principal process is transfer of fat from the lumen to the blood vessel wall (especially the elastic tissue) but this type of study does provide basic information of undoubted significance for the elucidation of lipid interchange and deposition in vessel wall

Electron microscopy is still in the earliest stages of development Its present rate of growth suggests an embryonic rather than even an infantile phase of evolution but its potential importance cannot be overemphasized The purpose of this note is to draw attention to this newcomer to the family of technical auxiliaries in the study of the structure of coronary vessels and of coronary disease

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REFERENCES

1 Buck, R C Fine structure of aortic endothelial lesions in experimental cholesterol atherosclerosis of rabbits Am J Path 34 897 1958

Fawcett, D. W., and Selby, C. C.: Observations on the fine structure of the turtle atrium, J. Biophys. & Biochem. Cytol. 4:6.., 1958.
Karrer, H. E.: The ultrastructure of mouse lung, J. Biophys. & Biochem. Cytol. 2:241, 19.6.
Lewis, W. H.: Pinocytosis, Bull. Johns Hopkins Hosp. 49:1.., 19.1.
Moore, D. H., and Ruska, H.: The fine structure of capillaries and small arteries, J. Biophys. & Biochem. Cytol. 3:45.., 1957.
6. Palade, G. E.: Fine structure of blood capillaries, Appl. Physics 24:14.4, 1953.
7. Parker, F.: An electron microscope study of coronary arteries, Am. J. Anat. 103:..4, 1958.
8. Parker, F.: An electron microscopic study of experimental atherosclerosis, Am. J. Path. 35:19.., 1960.

Letter to the Editor

Digital computer analysis of the electrocardiogram

Institute of Physical Medicine
and Rehabilitation
400 East 34th Street
New York 16, N. Y.
September 12, 1960

To the Editor:

This communication is to announce the availability of a general purpose computer program for a machine abstraction for electrocardiograph wave amplitudes, durations, and areas from scalar leads. The program was written for an IBM 650 digital computer. Input [illegible] must be in digital form taken at equal time intervals of [illegible] milliseconds or more. Up to three scalar leads can be processed simultaneously.

Output data present (1) the equation for the reference "isoelectric line," (2) the timing of each wave beginning, ending, and maximal amplitude for all positive and negative waves about an arbitrary magnitude to be set by the investigator, (3) the maximal wave amplitude, relative wave areas, and ST-segment displacement information and timing.

A more detailed 15-page operating manual will be provided upon request.

The author received encouragement and support from the Heart Control Program and from the National Heart Institute, United States Public Health Service.

Lee D. Cady, Jr., M.D., D.P.H.

Book reviews

ELECTRON MICROSCOPY OF THE CARDIOVASCULAR SYSTEM A ELECTRON MICROSCOPIC STUDY WITH APPLICATIONS TO PHYSIOLOGY B Bruno Kisch M D Professor and Medical Director Yeshiva University Director Electron Microscopic Research Institute Elmhurst City Hospital t New York Professor Emeritus University of Cologne Cologne Germany Translated from the original German text by Arnold I Kisch M D New Haven Conn Springfield Ill 1960 Charles C Thomas 180 pages Price $ 50

The title of th book is somewhat misleading be cause from it one expects a description t the electron microscopic level of the entire cardiovascular system Actuall no part of the cardiovascular system except the heart is even touched upon.

A large part of the book is devoted to the ultrastructure of muscle both skeletal nd cardiac An attempt is made to review some of the earlier work on muscle but the a thor gives insufficient recognition to the real pioneers in the electron microscopic stud of muscle. I his discu ion of muscle fiber the uthor dwell t length on myofibrils sarcosomes (mitochondria) striations and nuclei however he barely touches on the endoplasmic reticulum which an important component of muscle as well as of other types of cell and which has been studied extensively with the electron microscope

This book actually reviews of the author own work of the last ten years t hich he add his own (sometimes questionable) interpretations of the work of other Nomenclature is incon sistent nd the wording is poor so that t is often difficult to nderstand the uthor meaning

Apparently the many electron photomicrographs used in the book were all from the uthor laboratory The quality of the micrographs ranges from good to poor

ELECTROPHYSIOLOGY OF THE HEART By Brian F Hoffman M D Associate Professor of Physiology College of Medicine State University of New York Downstate Medical Center Brookl N Y nd Paul F Cranefield Ph D Associate Professor of Physiology College of Medicine State University of New York Downstate Medical Center Brookly N Y New York 1960 McGraw Hill Book Company Inc 323 pages Price $12 50

This book summary of ailable information bout the tra membrane potentials of single cardiac fiber as registered by microelectrode techniques much of it previously published After introducing the method and the Hodgkin ionic theory of the action potential the authors have systematically described the characteristics of the action potential found in the major types of cardiac fibers (trial entricular sinoatrial nodal atrioventricular nodal and Purkinje) and the effects of physiologic ariables upon each

The text lucid and the presentation logical and straightforward A wide udience has been kept in mind by the sound early introduction of preparatory definition However one exceptional obstacle to clarity for the general reader in the field of cardiology was noted the term *regenerative depolarization* was frequently encountered and never adequately defined Careful comparison of contexts allowed the inference that both local and propagated responses were included and that *regenerative* was used in the sense of *autoacceleration* but the electronic basis for such usage as not made clear

The reviewer strongly recommends this book to the serious student of the electrical behavior of cardiac muscle whether he be biophysicist physiologist or physician

EDEMA MECHANISMS A MANAGEMENT Edited by John H Moyer M D Professor and Chairman Department of Medicine Hahnemann Medical College and Hospital and Morton Fuchs M D Assistant Professor of Medicine Hahnemann Medical College and Hospital Philadelphia Pa Philadelphia 1960 W B Saunders Company 833 pages Price $15 00

Many individuals contributed papers on various pects of the problems relativ to edema which formed the program of the Symposium on Edema Mechanisms and Management The papers are included in this monograph Some of the discussions are interesting and thought provoking whereas others are d ll or simply restate concepts of many ear duration without indicating the discrepancies between theory nd fact For example on pages 4 and 5 the tatement is made that the transcapillary hydrostatic pres ure which tend to promote los of ter from the tissue is equal to the oncotic pressure which tends to return the flu d The uthor then states that those who came to the Symposium on bus had their legs dow for long time After introducing this concept he fails to indicate why all of them did not ha their legs greatly distended with edema fluid knowing how rapidl fluid and electrolytes tra erse the capillary wall Nor does he point out hy it is if transcapillary hydrostatic and oncotic forces are equal and transcapillary fluid exchange imply regulated by such forces that all people are w thout gross evidence of edema of the legs all day h tall people do not normally ha much more edema of the ankles and feet than short ones or why patients hav high enous pressure w thout clinical evidence of edema If symposium is to settle

questions the fundamental problems should be constantly before the participants and clearly defined Conventionally accepted concepts and theories which fail to explain established observations should be presented with apologies and warning or be presented to show their inadequacies Old errors and discrepancies should not be repeated constantly without regard for *the need to elucidate them*

The chapter on the lymphatic system and its influence on extracellular fluid balance is no more mature or thought provoking than a brief comment made to freshman medical students or to premedical students in a class of zoology The mature members of the audience must have been extremely bored Few of the many important questions that could have been asked and answers that could have been discussed Furthermore little effort was made throughout the monograph to indicate what the original observations were and who made them This Symposium also reflects another trend in American medicine to abandon well tested therapeutic procedures for new ones which have not been adequately evaluated For example the papers on the treatment of the edema of congestive heart failure de-emphasize the use of mercurial diuretics which are still excellent and are usually more effective than the new ones such as the chlorothiazide type of preparations which have important subtle harmful effects which are sometimes fatal This approach is due in part to the fact that some who wrote on the management of the disease states are not experienced clinicians and cardiologists who have daily responsibilities to patients but are primarily laboratory investigators

Some papers are brief and the statements made are not documented with research data This is particularly true of the article on forward and backward failure on page 704 which is more *philosophical approach than a discussion of* research The monograph consists of too many short notes on too many subjects few important problems were thoroughly or profoundly discussed

A number of the discussions were highly opinionated At times the moderator had to ask questions to keep the discussions in progress A number of the participants who were discussing complex problems in the formation of edema had not performed research for many years and had not been actively engaged in the study of the fundamental aspects of the formation of edema *This was reflected by the superficial nature of* the presentations questions and discussions

The sections on the kidney were better presented but they really added little that is new and failed to provoke any profound discussion

Medical students who might profit most from this book will find it impossible to orient the research and investigators in time and contribution In many instances experiments performed years before were merely repeated by modern methods and apparatus with far less imagination and thought

The purpose of the Symposium may have been achieved It would seem however that most symposia today devote most of their time to rehashing ideas already well known to the participants instead of embarking immediately on a few provocative presentations with much discussion to consider thoroughly only a few problems rather than the entire field Anyone invited to attend such a symposium should be expected to know the usual concepts or he would not qualify for invitation Perhaps we need fewer but more mature symposia This book makes available to researchers of the world the discussions presented at a representative type of mid twentieth century symposium on a special subject in clinical medicine

If the reader wishes a conventional summary of tidbits on edema he will find the book useful A medical student or anyone beginning a study of the formation and management of edema will find this book to be a start in his reading *If he is engaged in research in the field he will* find it necessary to read a great deal before he discovers an interesting or new point

GRUNDRISS UND ATLAS DER ELEKTROKARDIOGRAPHIE By Rudolf Zuckermann Dr med habil Facharzt für Kardiologie Oberarzt an der Kinderklinik der Martin Luther Universität Halle-Wittenberg und Leiter der kardiologischen Abteilung Professor mit Lehrauftrag für Kardiologie Third edition Leipzig 1960 Georg Thieme 620 illustrations 660 pages Price geb DM 72 15

This book was first published in 19 5 under the title *Atlas der Elektrokardiographie* Since then it has been expanded as the *Grundriss und Atlas der Elektrokardiographie* and now covers about 650 pages As mentioned in the foreword of the first edition it is based on the personal experience gained by the author at the Institute of Cardiology in Mexico

Electrocardiographic theory is summarized and takes up only 18 pages This is followed by a rather large section which covers the different lead systems A section on vectorcardiography describes the principle the main lead systems and some schematic vectorcardiograms of normal subjects of patients with right and left hypertrophy as well as of patients with right and left bundle branch block The the normal ECG its variations and its measurements are described Also the pathologic ECG is summarized with several instructive schemata The atlas contains several examples of electrocardiograms which are analyzed specifically and discussed extensively including the different forms of arrhythmias Finally a summary of the electrocardiograms of different animals is mentioned

This book cannot be judged as a textbook since the theoretical part presupposes the readers knowledge of the main principles which are not extensively discussed But the cardiologist will

find many interesting facts The author's tendency to use a special terminology makes the understanding rather difficult for non German readers He mentions for instance a normal P mitrale P pulmonale P congenitale bilateral enlargement of the atrium P infantile tension P hypertonic ST-depression and a so-called blocking QRS-complex in Lead V

ELECTROCARDIOGRAPHIC TECHNIQUE A MANUAL FOR PHYSICIANS NURSES AND TECHNICIANS By Kurt Schnitzer Second edition New York 1960 Grune & Stratton Inc 109 pages Price $4 75

The value of any book is determined by its usefulness to its readers It is impossible to know the appeal of a book on this subject The intended readers are quite heterogeneous for physicians nurses and technicians differ widely in knowledge clinical responsibility and experience However the book must have proved useful since it is now in a second edition

The manual includes a brief discussion of cardiac terminology the electrocardiogram the electrocardiograph the technique of recording and mounting tracings and other obvious considerations of a subject of this nature

Certain points are worth noting For example no mention of the qualifications and interest of the author is given on the title page Readers would like to know whether he is on the faculty of a medical school or the staff of a hospital and his title or rank The author fails to distinguish between his own ideas and the procedures of general practice and recommendations of procedure by responsible cardiologists and institutions e g the code used for marking each lead He fails to emphasize the need for care of the instruments the electrodes the heart station the records and other facilities which insure work of the highest quality The quality of electrocardiographic recordings depends upon good guidance experience and the high demand of the doctor and institution Most of the references in the bibliography are too technical specialized or controversial for nurses technicians and general physicians More useful references have been omitted

Vectorcardiography is not adequately presented The technique depends so much on the apparatus reference frame employed and objectives of the investigator that the subject should have been omitted until vectorcardiography is standardized for general clinical use

This manual can be of some value but it cannot replace careful training in the heart station clinic laboratory and at the bedside Nor can it replace the constant demands for high quality by a doctor who knows high quality electrocardiography

THE CLINICAL USE OF ALDOSTERONE ANTAGONISTS Compiled and edited by Frederic C Bartter M D Chief Section of Clinical Endocrinology National Heart Institute National Institutes of Health Bethesda Md Springfield Ill 1960 Charles C Thomas 211 pages Price $5 00

This book records the proceedings of a conference sponsored by G D Searle & Co in Chicago Ill Oct 16 1958 in which 23 investigators summarize limited experience with the 17 spirolactone steroids These drugs of which spironolactone (Aldactone Searle) is the most potent have been shown to antagonize the action of aldosterone on electrolyte excretion and as such they represent an interesting new class of diuretic agents aimed at reversing the contribution of hyperaldosteronism in sodium retaining disorders Their greatest effectiveness as natriuretic agents is in cirrhosis with ascites and the nephrotic syndrome conditions in which hyperaldosteronism has been shown to play an important role in the development and maintenance of edema The results in congestive heart failure are more tenuous although worthy of further study particularly since these drugs are most effective as *potentiators of the action of other* diuretics including the thiazides and mercurials Extensive clinical trial have been impeded by the scarcity of the compound and the relatively high cost of the drugs A clinically useful property of these drugs is that in contrast with other diuretic agents undesirable loss of potassium does not accompany the natriuresis and actual retention of potassium may be observed

The book is recommended for practitioners who treat patients with refractory edema of various etiologies and for those students and physicians interested in current research in sodium and water metabolism

ATRIAL SEPTAL DEFECT By H Gosta Dahlsen Copenhagen 1960 Ejnar Munksgaard 215 pages Price D kroner 50

The study of congenital heart disease has progressed so much in the last decade that few will be surprised to find a sizable monograph devoted solely to the subject of atrial septal defect In this work the pertinent literature up to 1 a has been carefully reviewed and integrated with an account of 132 cases studied personally by the author The subject is covered exhaustively including a careful account of the embryologic development of the atrial septum and a tabular summary of 190 autopsied cases gathered from the literature The cases of the author were studied in Rigshospitalet the University Hospital of Copenhagen Twenty per cent of

patients were found to ha tight mitral te-nosis This group included patients in whom the mitral orifice was too small to admit two fingers and those with retraction of the al e or thickening and shortening of the subval ar apparatus Such lesions were not associated with a clinical history of rheumatic fever and were much more frequent in patients over 30 years of age The trial septal defects were usually in th central portion of the auricular septum Secondary development of the septal defect could not be ubstantiated Differences mean trial pressure are believed by the author to pl central role determining the degree and direction of hunting but confirmatory evidence is lacking—possibly beca se of tech nical difficulties in measuring trial pressure gradients

The English style is clear and readable The printing and format are excellent but the use of flimsy paper over is regrettable This mono graph provides thorough and critical review of current knowledge of the anatomy ltered physiology and clinical manifest tions of a common cardiovascula defect It should be in the permanent library of every serious student of congenital heart disease

CARDIAC EMERGENCIES AND RELATED DISORDERS THEIR MECHANISM RECOGNITION AND MANAGEMENT B Harold D Levine M D Senior Associate in Medicine Peter Bent Brigham Hospital Boston Ma nd A sistant Clinical Professor of Medicine Harvard Medical School Clinton Mass 1960 The Colonial Press Inc 381 pages 44 illustrations Price $12

Thi monograph is devoted to the recognition and treatment of acut cardiac emergencies It includes chapters on acute left entricular failure cardiogenic shock cardiogenic chest pain episodes of tachycardia and arrh thmia as well as Adams Stokes disease syncope cardiac arrest nd re suscitation The primary empha on the linical pproach t recognition of these problems nd on practical mea ures of treatment The thor evidentl ha draw extensively both pon h own clinical experience nd that of his associates

A bibliography is included which while not encyclopedic will be h lpf l to the reader N merous helpful points both clinical and elec trocardiographic are made in the diagnosis of cardia arrhythmia nd tachycardias

I some nstances the uthor has apparently taken some liberties in expressing his opinion about matters which may be controversial Thus i regard t the use of asopressor substances in cardiogenic shock is his tatement that Withal it must be conceded that there is no overwhelm ing tatistical evidence for the alue of these drug Onl a occasional patient is salvaged Such tatement cannot be con idered repre sentativ of extensi sampling of the result reported in the recent literature Likewise the section concerning acute myocardial infarc tion he states The common practice of routine hourly or two-hourly blood pressure determina tions around the clock is superfluous nd deprives the patient of badly needed rest This i de batable in the opinion of the re iewer If ny thing more caref l mo toring of blood pre sure level and arrhythmias even by electronic and mechanical mean is needed order to dete t the early ppearance of these omplications th disease Such careful observ tion with early recognition of these berrations ma indeed be lifesa ing

There re also many experienced clinicians who will probably take is ue w th the view that Starting early as the first or second da long as he is not hock the patient w th cut myocardial infarction should be out of bed eated well padded chair for as many hours of the da as he w ll tolerate This armchair treat ment has been the basis for much stimulating discussion Although some studies suggest that this treatment is beneficial final evidence that it improves the morbid ty and reduces the mor tality is yet however w nting The a thor would ha e done better to indicate that this latter therapy is still somewhat *sub jud*

The olume is ell written replete w th good clinical experience and will be aluable to stu dents house officers nd pract tioners generally It should be helpful t nyone who ha to deal with acute cardiac emergencies

Announcements

Awards totaling $30,000 for medical work in arthritis and heart disease were announced today by J. A. Gairdner, Toronto industrialist and financier and President of the Gairdner Foundation, Toronto, Canada.

Four American and two British medical scientists have the award and each will receive a prize of $5,000. The winners are:

Dr. John H. Gibbon, Jr., Professor of Surgery and Director of Surgical Research, Jefferson Medical College, Philadelphia, in recognition of Dr. Gibbon as the first man to develop and successfully use an artificial heart for the surgical correction of heart defects in human beings.

Dr. William F. Hamilton, Professor of Physiology, University of Georgia School of Medicine, for his work with the use of dyes injected into the blood stream to determine blood flow and distribution in the treatment of heart disease.

Dr. Karl Meyer, Department of Medicine, Columbia University, New York, for his contributions to the modern concept of the chemical structure and functions of the so-called binding substances of connective tissues and supporting structure of the body and part of inflammatory processes involved in rheumatic and other diseases.

Dr. Arnold R. Rich, Baxley Professor Emeritus of Pathology, Johns Hopkins University, Baltimore, for his major investigations into the allergic responses to drugs used in the treatment of certain rheumatic and other diseases.

Dr. John McMichael, Professor of Medicine, University of London, as the first man in England to apply the technique of cardiac catheterization and through this investigation to make a major contribution leading to the fuller diagnostic accuracy required in heart surgery.

Dr. Joshua H. Burn, retired Professor of Pharmacology, Oxford University, for outstanding contribution to knowledge of the action of drugs in cardiovascular disease.

The Gairdner Foundation was incorporated in 195 and its funds are derived from personal gifts of Mr. Gairdner and his family. Mr. Gairdner was President of The Canadian Arthritis and Rheumatism Society from 1949 to 195 and Chairman of its National Board of Directors from 1952 to 1958.

Mr. Gairdner said that the awards are prizes for achievements and not grants for the support of future research. Awards are intended to encourage and reward individuals who have made major contributions to the conquest of disease and human suffering, to help focus attention on the problems of arthritis and heart disease and to facilitate communication of ideas among scientific workers in these fields.

Last year's award winners were Dr. Alfred Blalock and Dr. Helen Taussig of Baltimore, Dr. Harry Rose and Dr. Charles Ragan of New York, Professor W. D. M. Paton and Professor Eleanor Zaimis of Oxford and London, England, respectively, and Dr. W. G. Bigelow of Toronto.

Applications for Charter Membership in The American Society of Diagnostic Radiology are now being received. Membership is open to cardiologists, chest physicians, gastroenterologists, rheumatologists, orthopedists, pediatricians, otolaryngologists, internists and general practitioners *who do or may desire to do some type of diagnostic radiology in their offices.*

For further information write to Louis Shattuck Baer, M.D., Secretary, The American Society of Diagnostic Radiology, 411 Primrose Road, Burlingame, Calif.

The following statement by Leroy E. Burney, Surgeon General, U.S. Public Health Service, on INFLUENZA IMMUNIZATION is reproduced from *Public Health Reports*, Public Health Service, U.S. Department of Health, Education, and Welfare, Vol. 75, No. 10, p. 944, October 1960.

The outbreak of influenza that swept the United States in the fall of 1957 and the winter of 1958 resulting in 60,000 more deaths than would be expected under normal conditions. There were in addition more than 26,000 excess deaths during the first 3 months of 1960 which also were considered to be the result of influenza.

These departures from the usually predictable norms prompted the Surgeon General's Advisory Committee on Influenza Research to analyze the cause and to seek measures to prevent their recurrence in the future.

The committee found that a new antigenic strain, because of its widespread introduction and the general lack of resistance to it, was the direct cause of the excess number of deaths not only in the total population but most markedly among the chronically ill, the aged, and pregnant women. As a result of these findings, the Public Health Service is urging a continuing program to protect these high risk groups in order to prevent a recurrence of this excess mortality.

The high risk groups who contribute most to the excess deaths and who the Public Health Service believes should be routinely immunized each year are:

1. Persons of all ages who suffer from chronic debilitating disease, in particular (*a*) rheumatic heart disease, especially mitral stenosis; (*b*) other cardiovascular diseases, such as arteriosclerotic heart disease or hypertension—especially patients with evidence of frank or incipient insufficiency; (*c*) chronic bronchopulmonary disease, for example chronic asthma, chronic bronchitis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema, or pulmonary tuberculosis; (*d*) diabetes mellitus; (*e*) Addison's disease.

2. Pregnant women.

evidence in favor of the role of *Rickettsia prowazekii* in the constitution of certain subacute endocarditides and certain instances of thromboangiitis of the Buerger type

On the contrary for two or three decades other forms of heart disease have been constantly increasing in incidence in Algeria Among these are arterial hypertension arteriosclerosis and rheumatic heart disease An increase in the incidence of these diseases can be explained by the fact that the present heart disease in the Mussulman population is falling more and more into line with that of the populations of European countries whereas until World War I the Mussulman population had been almost completely exempt from these forms of heart disease

Thus formerly a high blood pressure in a Mussulman of North Africa was diagnostic of glomerulonephritis Today the apparently primitive *hypertensive disease* is frequently observed among the Mussulmans who live in the towns and those who work in the capital but is seen infrequently among the rural population It appears to us that the agitation and overcrowding of the cities the noise the irregularity of work hours and especially the night work play a more important pathogenic role than do quantitative and qualitative changes in the diet

What is true for arterial hypertension is also true for angina pectoris peripheral arteritis and in general all forms of atheroma It has become a truism to say that the development of hypertension and atherosclerosis among the Mussulmans is parallel to the extension of occidental civilization

But the pathologic evolution of rheumatic fever which represents the most frequent cause of heart disease in Algeria is undoubtedly the most striking For this reason and because of a more complete personal documentation in this than in any other area of cardiology we will discuss this subject in more detail

It is known that the geographic distribution of this disease has for a long time appeared to be uneven frequent in temperate countries and rare in the hot regions of Africa Asia and Oceania North Africa which is situated at the limits of the temperate and the subtropical regions was no exception to this rule the incidence of rheumatic fever was much lower in this country than in metropolitan France

In 1905 Dumolard and Lemaire[1] mentioned the extreme rarity of rheumatic fever among the natives and cited a study of Gros who had observed only 4 or 5 cases of valvular heart disease among the 10 000 natives whom he examined Andrieu[2] in his thesis in 1926 reported army statistics for the 5 year period 1908 1912 which showed that the rheumatic morbidity in Algeria was 9 26 per 1 000 or less than half of the morbidity observed among the troops stationed in metropolitan France The incidence of rheumatic fever in the European and in the Algerian native as deduced from the figures published by Fabiani[3] in 1932 by Aubry and Thiodet[4] in 1937 and from data collected in the Clinique Medicale Infantile d Alger was as follows 14 2 per 1 000 in the European adult 19 3 per 1 000 in the European child of 3 to 15 years of age 3 per 1 000 in the Mussulman adult and 4 2 per 1 000 in the Mussulman child In all, these works attest the rarity of rheumatic fever in the Algerian native The role of the climate was of little importance as evidenced by the fact that the incidence of rheumatic fever in the European living in Algeria was as high as that in metropolitan France

But in the last 20 years this notion has had to be revised as early as 1939 Combe[5] wrote that rheumatic fever and its cardiac complications were far from exceptional in the Mussulman child Venezia[6] in studying the files of the Clinique Medicale d Alger from 1944 through 1950 showed that the incidence of rheumatic fever (arthritis chorea or rheumatic heart disease) was 28 per 1 000 of the Mussulman children of 5 to 15 years of age who were hospitalized during that 7 year period This figure is comparable to those published by Grenet[7] in 1949 who reported that in France of all the children hospitalized in the departments of internal medicine an average of 20 to 45 per 1 000 had rheumatic fever

We have resumed this study during the last 8 years from 1951 to 1958 We have retained only the authentic cases of rheu

matic fever and purposely omitted the cases of chorea Our findings show a high percentage of rheumatic fever about 95 per 1 000

Although our statistics may be criticized they undoubtedly reflect an increase in the incidence of rheumatic heart disease In a hospital ward of 50 patients who ranged in age from 5 to 15 years it is not rare to find that one third of the patients have valvular heart disease

The second fact to be emphasized is the severity of the disease as is shown by the frequency of the recurrences and deaths For a total of 323 patients we recorded 451 admissions to the hospital some patients had been admitted several times some up to seven or eight times during these 8 years We have recorded 29 deaths which is a very high figure for a group in which several patients had originally only articular involvements without cardiac manifestations

Those are the facts How can they be explained? One might wonder whether the increase in morbidity is not due to the fact that the native more readily seeks medical advice as he becomes adapted to European civilization But this argument cannot be upheld since the figures reported express the percentage of admissions for rheumatic fever in relation to the total number of admissions in the same hospital Moreover the climate race and constitutional factors do not seem to have the importance that has been assigned to them by some authors

Most of our patients are natives of large cities very few come from the country The city of Algiers alone provides more than half of the patients Thus the most likely cause of the increase in rheumatic morbidity may be found in the economic and social transformation of the Mussulman masses and consequently in the demographic evolution of the country This evolution is characterized by the increase in the native population and the immigration of the rural Mussulman population to the cities

The native population of Algeria is increasing rapidly it numbered 3 000 000 individuals in 1830 7 300 000 in 1948 and 9 250 000 in 1958 The urban population as represented by the inhabitants of 46 cities was 226 000 Mussulmans in 1886 1 398 000 in 1954 and 1 700 000 in 1958 Thus whereas the total population has increased three times the urban population was increased eight times In the city of Algiers the population was estimated to be 13 000 Mussulmans in 1866 226 000 in 1946 and 420 000 in 1959 The population increases at a rate of 5 per cent annually

The two consequences of this immigration to the cities are (1) a dense population often living in conditions of poor hygiene and (2) a closer relationship of the Mussulman population with the European population which originally was more often subject to rheumatic fever

Actually since the onset of the disturbances which have troubled Algeria many fellahs (especially peasants) have left the land in order to come and find refuge in the large cities where they feel more protected from terrorism And in studying our figures we see that it is precisely since the year 1954 that the incidence of rheumatic fever has greatly increased

Can these demographic data explain the severity of the disease in Algeria? Before answering this question one must wonder whether there is not an epidemic genius special to the country There is no clinical or bacteriologic evidence in favor of this hypothesis In 1958 Raoux[9] made a complete biologic survey of 51 patients Each patient was subjected weekly to laboratory studies including determination of the sedimentation rate fibrinogen total polysaccharides hexosamines blood and urinary mucoproteins C reactive proteins antistreptolysin titer proteinogram lipidogram and glucidogram The results were comparable to those published in France and elsewhere in Europe

Nor can mistakes made in the matter of therapeutics be incriminated because all of the children received a standard treatment combining antibiotics and hormones Treatment of the attack was in each case followed up by maintenance treatment with long acting penicillin and salicylates But the prophylactic treatment with penicillin is in most cases abandoned as soon as the children leave the hospital Moreover these children

not find at home the conditions of hygiene and rest required for a complete cure of the disease. Complete bed rest is almost impossible to realize at home.

Thus the evolution of rheumatic fever in Algeria illustrates strikingly the transformation of the cardiovascular disease in this country. It has given rise to new problems the importance of which has not escaped the Public Services.

REFERENCES

1. Dumolard L and Lemaire G Bull Méd de l Algerie 3 649 1905
2. Andreu C Thèse Toulouse 1976
3. Fabiani G Le problème des endocardites et la pathologie cardiaque chez l indigène musulman Alger 1932 Delmas
4. Aubry G and Thiodet J Algerie Méd 116 423 1937
5. Combe P Thèse Alger 1939
6. Véneroni R Thèse Alger 1950
7. Grenet H La maladie de Bouillaud Paris 1949 Flammarion
8. Breil J La population en Algerie Tome II Documentation française Paris 1954
9. Raoux, J P Thèse Alger 1958

Clinical communications

Complete left bundle branch block
A physiologic-pathologic correlation
Report of a case

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We have recently had the opportunity of examining the heart at autopsy of a patient who electrocardiographically showed complete left bundle branch block and in whom simultaneous catheterization of both ventricles revealed no delay in onset of left ventricular systole. This afforded us the opportunity of studying the conduction system and the entire heart to ascertain the anatomic substrate of this form of complete left bundle branch block.

Case report

Clinical history This 49-year-old woman was first seen on June 6 1955 at the clinical center of the National Institutes of Health for evaluation of rheumatic heart disease. The patient remembered no definite signs or symptoms of rheumatic fever. She did have frequent upper respiratory infections in childhood which decreased in frequency after tonsillectomy. Six to 8 years before admission she noted insidious onset of shortness of breath. Three years before admission she felt weak and was treated for liver trouble and ulcers of the stomach. Her shortness of breath became worse at this time and was accompanied for the first time by ankle edema and ascites. She was placed on digitalis, low-salt diet and bed rest and she responded well until 1 year ago when she had an episode of pulmonary edema. This responded to treatment and she was well except for shortness of breath on moderately severe exertion.

Physical examination On this first admission the heart was found to be enlarged to the anterior axillary line. The heart sounds were faint and distinct. The blood pressure was 130/80 mm Hg. The liver was enlarged. Extensive laboratory examination was essentially negative. The electrocardiogram revealed complete left bundle branch block (Fig 1). Chest film and cardiac fluoroscopy showed cardiac enlargement laterally and downward which was considered to be left ventricular. The aortic arch was smaller than normal. The distal portion of the esophagus was displaced to the right by the ventricular enlargement. Angiocardiogram showed the left ventricle to be grossly enlarged with no radiographic evidence of shunt. Left and right heart catheterization showed no evidence of shunt nor mitral regurgitation or stenosis. Liver biopsy was negative. The patient was discharged on July 20 1955 being on digitoxin beta vitamins phenobarbital Seconal and Neohy[illegible]

She re-entered the hospital on Dec 19 1955 because of persistent shortness of breath and fatigue. Physical examination now revealed blood pressure of 112/62 mm Hg. A scratchy systolic murmur was heard along the left sternal border and there was a Grade 2 apical systolic murmur and a questionable diastolic gallop. The liver was again palpable. The ECG again showed complete left bundle branch block.

Simultaneous right and left heart catheterization (Fig 2) performed by Dr Eugene Braunwald revealed slight elevation of the right ventricular pressure (32/7 mm Hg) and marked elevation of the left ventricular end diastolic pressure to 25 mm Hg. The time interval between the onset of ventricular depolarization [illegible] the beginning of the QRS complex and the onset of left ventricular contraction [illegible] the onset of the systolic rise of left ventricular pressure was 0 075 second. The onset of left ventricular contraction followed the onset of right ventricular contraction by only 0 010 second in some beats and in other portions

F[illegible] the Cong[illegible] H[illegible] Dunger Resea[illegible] and Training C[illegible] H[illegible] Chicago Ill
This study was supported by Research Grant H-[illegible] from the Nat[illegible] Heart Institute of the N[illegible]
[illegible] Health U S P H S Bethesda Md
Received for publication [illegible] 1960



Fig 1 Electrocardiogram showing complete LBBB

of the tracing the onset of contraction in the two ventricles was identical The duration of left ventricular contraction exceeded that of right ventricular contraction Normal values for the relationship between electrical and mechanical events were presented by Braunwald F hman and Cournand

The patient was discharged from the hospital on Jan. 20 1956 with the diagnosis of idiopathic myocardial hypertrophy She returned to Miami Florida where she was found dead on Feb 27 1957 Her history between discharge and death is unknown

Postmortem examination Only the heart was available for study (Fig 3) This weighed 750 grams embalmed The right atrium was slightly hypertrophied The tricuspid orifice was markedly dilated The distance between the orifice of the coronary sinus and the annulus of the tricuspid orifice was larged The edges of the medial and anterior cuspid leaflets showed diffuse thickening which involved the chordae The right ventricle was slightly hypertrophied and its chamber was dilated The pulmonic orifice was slightly dilated and its valve showed increased hemodynamic change. The left atrium was markedly hypertrophied and moderately dilated The mitral valve howed the usual changes of aging and the mitral orifice was normal The left ventricle was tremendously hypertrophied and markedly dilated The endocardium of the left ventricle was in general thicker than normal In addition 3 and 5 cm respectively from the commissure between the right and posterior aortic cusps there were two localized thickenings the proximal one with a diastolic pocket. The aortic orifice was normal in size As to the aortic valve the adjacent parts of the right and posterior aortic cusps were thickened and there was an adhesion between them below where the commissure should have been There was no exact commissure between the adjoining edges The remainder of the valve showed the usual changes of aging with slight widening of the commissure between the left and posterior cusps The right circumflex and the left anterior descending coronary arteries presented only occasional plaques and no narrowing The left circumflex could be followed only in its beginning and showed no narrowing

The internal measurements of the heart were as follows tricuspid orifice—12 7 cm pulmonic orifice—7.5 cm. mitral orifice—8 0 cm aortic orifice—7 0 cm. right ventricle inlet length—9.3 cm outlet length—11.5 cm left ventricle inlet length—9.5 cm. outlet length—10.3 cm

Microscopic examination The entire heart including the conduction system was studied in a manner previously described The S-A node and its approaches the A V node and its approaches and the penetrating portion of the A V bundle were serially sectioned and every twentieth section was retained The branching portion of the A V bundle with the origin of both bundle branches were serially sectioned and every tenth section was retained The remainder of the bundle branches up through the keel of the moderator band was serially sectioned and every twentieth section was retained The bases of the anterior and posterior papillary muscles were serially sectioned and every fortieth section was retained The region containing the ramus ostii cavae superioris was serially sectioned and every eightieth section was retained The remainder of the atrial and ventricular septa and the entire parietal walls of the atria and ventricles were cut into blocks and two sections were taken from each block These sections were alternately stained with hematoxylin-eosin and Weigert van Gieson stains Thus a total of 1 297 sections were studied

GENERAL PATHOLOGIC CHANGE There was an acute vascular degeneration associated with a mild perivascular fibrosis throughout the myocardium of both ventricles atria and the atrial and ventricular septa Occasional macrophages were infiltrated in the perivascular spaces The fat tissue at the base of the ventricles in the A V grooves showed a fine infiltration of mononuclear cells with growth of young connective tissue Focal fibroelastic thickening was present in the endocardium of the left ventricle

Left ventricle anterior wall There was subendocardial fibrosis with small scars more prominent in the apical than in the basal half This involved the anterior papillary muscle

Left ventricle posterior wall Small zones of subendocardial fibrosis were less numerous here but the posterior papillary muscle showed considerable fibrosis with small scars

Right ventricle anterior wall There was marked fatty infiltration

Right ventricle posterior wall Aside from the generalized pathology there was no change

Ventricular septum There was an elastosis of the myocardium at the base The left side of the ven

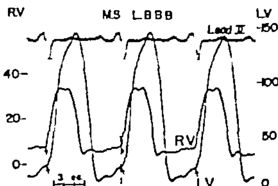


Fig 2 Pressure tracing showing no delay in onset of left ventricular systole

tricular septum showed marked fibroelastic thickening of the endocardium with scattered accumulations of lymphoid cell beneath the endocardium Zones of fibrosis and small scars were present beneath the endocardium and were most numerous and large in the mid anterior and apical portions of the septum There was an occasional eccentric thickening of an arteriole

Atria The left atrium showed foci of lymphoid cells beneath the endocardium Both atria presented few such accumulations in the wall In addition in the right atrium there was considerable fatty infiltration beneath the endocardium and the wall with hemorrhage in the epicardium and myocardium in the appendage Here also there was focal thickening of the epicardium with an infiltration of lymphoid cells

Aortic valve There was no evidence of old endocarditis (Fig 4) Section through the peculiar commissure showed hemodynamic changes[4] with zones of degeneration and small infiltration of mononuclear cells

Mitral valve In addition to the ordinary changes due to aging the ventricular at the base of the mitral valve showed proliferation of the endothelial lining and an infiltration of neutrophils There was no evidence of old endocarditis

Tricuspid and pulmonic valves These showed increased hemodynamic changes but no evidence of old endocarditis

Conduction system S A node—The node was considerably surrounded by fat but not isolated Otherwise no change was noted Approaches to S-A node—Here there were foci of hemorrhage Approaches to the A V node—Here there was marked infiltration of fat with few lymphoid cells and eosinophils A V node—Slight fatty infiltration was present A V bundle penetrating and branching—Fatty infiltration was present An occasional arteriole was narrowed There was marked fibrosis of the left side of the bifurcation.

Left bundle branch The changes here were related to the changes in the central fibrous body and the adjacent ventricular septum The central fibrous body was elongated and sent large shoots into the base of the ventricular septum both the left and the right sides Some calcification was noted on the right side The pars membranacea likewise



Fig 3 Aortic valve showing peculiar cusp formation Arrow points to jet lesion.

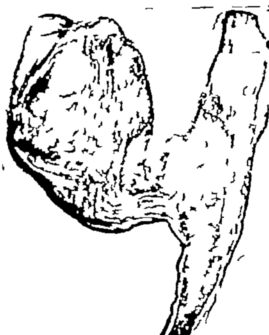


Fig 4 Photomacrograph of the small cusp-like formation of the aortic valve showing the coral reef appearance of the hemodynamic changes Weigert-van Gieson stain X 25

showed fibrous thickening with hyalinization on the left side On the left side the endocardial and subendocardial regions of the base of the ventricular septum were thus replaced by thick hyalinized connective tissue (Fig 5) The beginning of both the anterior and posterior radiations of the left bundle branch was thus interrupted (Fig 6) Only a few solitary strands of fibers were seen proceeding in this area Since every tenth section was saved in the serial sectioning of this area it cannot be stated whether the interruption of the left bundle branch was complete More distal to this region fibers of the left bundle branch were seen both in the anterior and the posterior radiations They appeared to be smaller than normal (Fig 7) being about the size of myocardial cells There were zones of fibrosis throughout

Right bundle branch The first portion showed occasional small zones of fibrosis which replaced less than one tenth of the muscle in any section The second and third portions were normal The right bundle branch was followed into the moderator band

Pathologic diagnosis of the heart (1) Congenital malformation of the aortic valve with aortic insufficiency (2) Focal endocardial fibroelastosis of the left ventricle (3) Subendocardial fibrosis with small scars of the left ventricle (4) Hypertrophy and dilatation of the left atrium and ventricle marked right ventricle moderate and right atrium slight (5) Fibrosis of the base of the ventricular septum (6) Severe fibrosis of the beginning of the left bundle branch (7) Fatty infiltration of the right ventricle (8) Subacute inflammation of the atrium of the heart (9) Acute vascular degenera-

Discussion

This is apparently a case of an unusual type of congenital malformation of the aortic valve producing unusual effects. The malformation may be considered to be a tricuspid aortic valve with an unusual type of commissure formation or a quadricuspid valve. With advancing years and hemodynamic change this valve produced mild aortic insufficiency. The abnormal valvular formation with the insufficiency had striking hemodynamic effects. It led to focal endocardial hypertrophy (fibroelastosis)[4] and to fibrosis of the central fibrous body and the adjacent base of the ventricular septum. The latter was responsible for the lesion of the left bundle branch.

In the absence of coronary disease and healed myocarditis in our present knowledge a possible cause for the subendocardial fibrosis with scarring of the left ventricle is the fibroelastosis interfering with the arterioluminal and venoluminal circulation of the myocardium. This theory is supported by the much greater presence of both the fibroelastosis and the scarring in the anterior and mid portion of the septum than in the posterior basal portion of the septum. Thus an ischemic lesion is postulated to be superimposed on the mild aortic insufficiency thereby aiding in the production of hypertrophy and failure of the left ventricle. It is possible that another factor in the hypertrophy is the abnormal function of the left ventricle related to the left bundle branch block.

Concerning the correlation of the left bundle branch lesion with the physiologic findings it is to be noted that there was no delay in onset of left ventricular contraction. Yet the electrocardiographic findings were those of complete left bundle branch block. However there was a paradoxical relationship in the closure of the semilunar valves: the pulmonary valve closed before the aortic. Braunwald and Morrow have previously postulated the following hypothesis for the explanation of this: "A conduction block may exist in the branches of the left main bundle or within the left ventricular myocardium. Such a conduction disturbance would account for the prolongation and abnormal configuration of the QRS complex and also for the delay in the onset and termination of ventricular ejection. However since the onset of left ventricular contraction in these patients is normal a substantial portion of the left ventricle must begin to contract at a normal time and must therefore be depolarized at a normal time. Thus complete interruption of conduction could not be present."

It is unfortunate that our findings do not represent sufficiently useful data to shed light on this hypothesis. Since every tenth section of the origin of the left bundle branch was studied instead of complete serial sections we can only state that this was a severe lesion of the left bundle branch

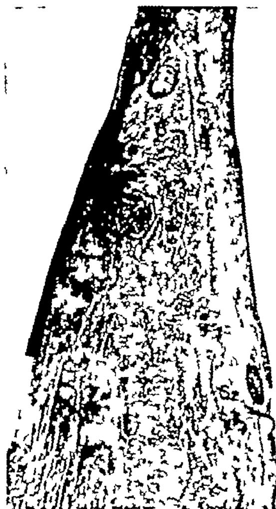


Fig. 5. Photomicrograph of the base of the ventricular septum. Hematoxylin-eosin stain ×20. B, Bundle of His. S, Scar on the left side of the muscular ventricular septum. S', Scar on the right side of the muscular ventricular septum. Arrow points to the region of interruption of the posterior radiation of the left bundle branch.



A



B

Fig. 6. A, Photomicrograph of the base of the ventricular septum at the beginning of the bifurcation. Low power view. Weigert-Van Gieson stain. ×51. *B*, Bundle of His. *L*, Anterior radiation of left bundle branch. Arrow points to the interruption. *B*, High power view of similar area showing fibrosis with infiltration of lymphoid cells. Hematoxylin-eosin stain. ×125.

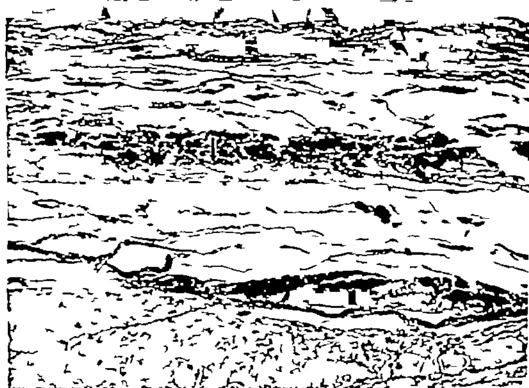


Fig. Photomicrograph of Purkinje fibers of left bundle branch showing small size. Arrow points to the Purkinje fibers. Weigert–van Gieson stain ×175

(90 per cent destruction) but we do not know whether it was a complete lesion. Likewise possible activation of the septum by Mahaim fibers from the A-V bundle cannot be completely excluded by this study, since every twentieth section was studied in the penetrating portion of the bundle and every tenth section in the branching portion, instead of complete serial sections. However, no Mahaim fibers were seen in the present method of sampling. Thus these anatomic studies do not answer the question of complete versus severe interruption of conduction to the left ventricle.

Nevertheless, this case of complete left bundle branch block has a distinct anatomic base. *There is severe interruption of the beginning of the left bundle branch with subendocardial fibrosis and small scars* in the hypertrophied and dilated left ventricle involving the papillary muscles. The genesis of this case of interruption of the left bundle branch is in accord with the findings of Lenègre,[6] who suggested that most of these lesions in the beginning of the left bundle branch are of a mechanical rather than ischemic nature.

Conclusion

A case is presented which electrocardiographically showed complete left bundle branch block and physiologically showed no delay in onset of ventricular systole but delay in onset and termination of ventricular ejection. Pathologically, there was a severe lesion of the origin of the left bundle branch produced by fibrosis and scarring of the central fibrous body, the pars membranacea, and the base of the ventricular septum. This was apparently related to abnormal hemodynamic effects of a congenitally malformed aortic valve.

I am indebted to Dr. Eugene Braunwald for permitting me to use the catheterization data, the illustrations of the electrocardiogram and the pressure tracings, and for his interpretation of this data. Also, I wish to thank Mr. Tomas R. Alvarez, B.S., A.S.C.P., for his technical assistance.

REFERENCES

1. Braunwald, E., Fishman, A. P.: A. Time relationship of dynam

cardiac chambers pulmonary artery and aorta in man Circulation Res 4 100 1956

2. Lev M and McMillan J B A semiquantitative histopathologic method for the study of the entire heart for clinical and electrocardiographic correlation AM HEART J 58 140 1959
3. McMillan J B and Lev M The aging heart II The valves (To be published.)
4. McMillan J B and Lev M The aging heart I Endocardium J Gerontol 14 268 1959
5. Braunwald E and Morrow A G Sequence of ventricular contraction in human bundle branch block a study based on simultaneous catheterization of both ventricles Am J Med 23 205 1957
6. Lenègre J Contribution à l'étude des blocs de branche comportant notamment les confrontations électriques et histologiques Paris 1958 J B Baillière et Fils (Arch mal coeur 50 (Suppl 1) 1 195)

Relationship of elevated blood pressure to ECG amplitudes and spatial vectors in otherwise "healthy" subjects

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The electrocardiogram is the most sensitive known indicator of left heart involvement in hypertensive patients, although its specificity leaves something to be desired. Increased QRS amplitude is believed to be the earliest manifestation of left ventricular hypertrophy, followed later by S-T, T changes. We have attempted here to determine whether moderate elevation of arterial blood pressure as often found in apparently healthy men is associated with characteristic differences in conventional electrocardiographic amplitudes and in spatial vectors.

Procedure

The study population consisted of 468 rural Finnish laborers who ranged in age from 20 to 60 years. Preselection involved elimination of respondents in the area who reported any history suggestive of heart disease, murmurs, hypertension, or other major physical impairment. Further selection was made for these items on the basis of findings at the time of medical examination. Indirect blood pressure was recorded at a single sitting, and subjects were included for analysis regardless of an isolated finding of elevated blood pressure if they were asymptomatic.

Blood pressure groups A, B, and C were assigned according to arbitrary cutoff values following the recommendations of the World Health Organization, and the number of subjects per group according to age are presented in Table I, along with relative weight and mean diastolic pressure, which was the value used in correlation analysis. In Group A were all subjects who had both a systolic pressure of less than 140 and a diastolic pressure of less than 90 mm. Hg. In Group B were subjects who had pressures of 140 mm. Hg systolic and/or 90 mm. Hg diastolic but under 160/95 mm. Hg. In Group C were all subjects who had pressures of 160 mm. Hg systolic and/or 95 mm. Hg diastolic or over. Eleven men had a systolic blood pressure that exceeded 180, and 12 had a diastolic blood pressure over 100, but no men who had a blood pressure of 200/110 mm. Hg or more were included.

Unipolar chest leads V_{3R} and V_1 through V_6 were recorded at the level of the fifth intercostal space in the mid-clavicular line

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Received for publication June [illegible] 19[illegible]

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[illegible] Laboratory of Physiological Hygiene, University of Minnesota, and Medical Director [illegible] Service [illegible] [illegible] Minn.

Table I

Age group	*Number of subjects*			*Mean relative body weight (%)*			*Mean diastolic blood pressure (mm Hg)*		
	A	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*
20–29	63	47	22	98 4	103 8	105 0	78	84	96
30–39	64	42	35	99 5	10 8	109 5	79	87	97
40–49	56	34	28	95 8	93 0	107 4	79	85	99
50–59	32	3	22	95 6	96 7	108 1	77	88	100

Under 140/90 mm Hg blood pressure
B 140/90–159/94 mm Hg blood pressure
C 160/95–199/109 mm Hg blood pressure

and leads to the right of V_{4R} were taken when necessary to secure the T wave transitional zone The leads were otherwise conventional and mean spatial QRS and T vectors were constructed with a mechanical analyzer previously described Data are given in terms of azimuth H (the horizontal plane vector in which 0 degrees points directly to the left) and elevation V° (the frontal plane angle representing the vertical elevation in which 0 degrees points straight down and 90° is the horizontal) vector magnitude (with 1 0 mm = 0 1 mv) and the spatial angle dA between mean QRS and T vectors

Results

Table II presents amplitudes of the R and T waves in Lead V and the magnitude of mean QRS and T vectors in the blood pressure groups There is a slight trend toward higher QRS amplitude and lower T amplitude of conventional measurements in Lead V_5 according to higher blood pressure categories The vector magnitudes also show differences between lowest and highest blood pressure groups but without a consistent trend In no case is the mean difference statistically significant except for the T wave in Lead V which is significantly lower in the high pressure Group C than in Group A

Correlation between the amplitudes of the T and R waves in Lead V is expressed by regression equations as follows

Group A $T_5 = 2\ 4 + 0\ 130 \times R$
Group B $T_5 = 2\ 5 + 0\ 106 \times R_V$
Group C $T_5 = 1\ 8 + 0\ 099 \times R_{V5}$

There is no significant difference in the slopes but the difference in intercept between lower and higher blood pressure groups (A and C) is statistically significant ($p < 0\ 01$)

Table III presents the data for azimuth (H) and elevation (V°) of mean QRS and T vectors and the spatial angle between these vectors (dA°) according to blood pressure grouping and the statistical significance of mean differences between the lower and higher blood pressure categories (C A)

There is no significant difference between groups in spatial orientation of QRS and T in the horizontal plane The angle of elevation of both QRS and T vectors is greater in the higher blood pressure group corresponding to a more horizontal electrical position The spatial angle of separation of mean QRS and T vectors is significantly greater in the higher pressure category (C)

The relationship of QRS elevation angle (V°) and age is given in Fig 1 for Groups A and C There is a significant though small positive correlation in elevated pressure in Groups B ($r = 0\ 287$) and C ($r = 0\ 236$) but none in Group A ($r = 0\ 122$)

Analysis of the relationship of QRS elevation angle (V°) and relative body weight reveals a significant positive correlation within blood pressure Group C ($r = 0\ 372$) but none in the normotensive Group A ($r = 0\ 129$) or in blood pressure Group B ($r = 0\ 133$)

Analysis of the QRS elevation angle (V°) in regard to age when relative body weight is kept constant reveals the persistence of a significant positive correlation in subjects with elevated blood pressure Group B ($r = 0\ 265$) Group C ($r = 0\ 252$) but none in Group A ($r = 0\ 093$)

Correlations between the elevation

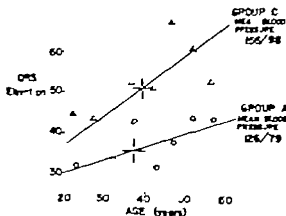


Fig. 1

QRS vector (V°), age, and relative body weight are expressed by regression equations as follows:

Group A V° = −23.3 + 0.46 × Age + 0.42 × Relative Weight

Group B V° = −41.7 + 0.81 × Age + 0.49 × Relative Weight

Group C V° = −52.0 + 0.64 × Age + 0.77 × Relative Weight

Fig. 2 shows the relationship of diastolic blood pressure and the angle between QRS and T vectors (dA°) for the entire sample of 468 healthy men. The correlation coefficient of this regression is 0.389. A significant positive correlation between this spatial angle (dA°) and relative body weight (r = 0.244) is found and as well between relative weight and diastolic blood pressure (r = 0.369). However, when diastolic pressure is kept constant there is no longer a significant correlation between the spatial angle (dA°) and relative weight. And when the body weight is kept constant, the significant positive correlation between diastolic blood pressure and the spatial angle dA° persists (r = 0.332).

Discussion

Attempts to apply criteria of ECG amplitudes in the individual diagnosis of left ventricular hypertrophy may result in considerable error in both missed and false positive diagnoses.[1] In general, however, among adult men a clinical relationship exists between large QRS waves, low T waves, and advanced hypertension. Recently Libretti and Zanchetti[4] studied a group of hypertensive patients with blood pressure over 200/110 mm. Hg and found that correlations which normally exist between QRS and T vectors decrease more or less in parallel with the severity of heart involvement. The data presented here suggest that a lower order of blood pressure elevation in putatively healthy working men results in myocardial changes of the same type but of lesser magnitude. The ECG findings in the higher pressure groups include significantly lower T wave amplitude, a significant difference in the intercept of the correlation between amplitudes of the R and T waves in Lead V_5, increased elevation of QRS and T vectors, and increased spatial angle between QRS and T vectors (dA°). The spatial angle between QRS and T vectors (dA°) is larger in subjects with elevated blood pressure in all age groups and there is also a definite regression toward a larger angle with progressive increase in diastolic blood pressure (dA° = 30.8 + 0.32 × diastolic blood pressure, Fig. 2). These findings may be the first sign of myocardial involvement in hypertension and appear prior to any significant increase in the magnitude of R waves or of the QRS vector.

Some of the ECG differences in higher blood pressure groups might be considered to be due to the influence of relative body weight, but statistical exclusion of the effects of relative body weight does not significantly alter the influence of blood pressure. However, the fact that there is a significant correlation between relative body weight and the QRS elevation angle only in the group with blood pressure over

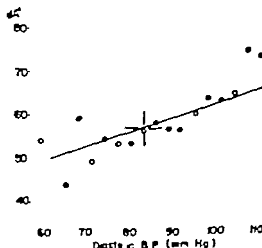


Fig. 2

Table II R and T wave amplitudes in chest lead V_5 (in mm) and magnitudes of the mean QRS and T vectors as related to the level of blood pressure

	Number of subjects	R_{V5} (mm)		T_{V5} (mm)		Magnitude of QRS		Magnitude of T	
		Mean	S D	Mean	S D	Mean	S.D	Mean	S D
Group A	215	18 3	6 16	4 8	2 05	10 4	4 49	3 6	1 36
Group B	146	19 5	6 69	4 6	2 16	10 2	3 91	3 6	1 32
Group C	107	20 4	6 23	3 8	2 00	10 7	3 54	3 3	1 37
Total	468	19 1	6 39	4 5	2 11	10 4	4 07	3 5	1 35

A Under 140 90 mm Hg blood pressure
B 140/90–159/94 mm. Hg blood pressure
C 160/95 199/109 mm Hg blood pressure.

Table III Mean QRS and T vectors azimuth (H°) and elevation (V°) and the spatial angle between them (dA) in 468 healthy men aged 20 to 60 years subdivided into three groups according to the blood pressure

	QRS-H		QRS V°		T H		T V°		dA	
	Mean	S D	Mean	S.D	Mean	S.D	Mean	S D	Mean	S.D
Group A	−28 4	15 4	33 9	17 5	+49 7	7 0	53 1	17 3	53 8	27 8
Group B	−27 1	18 7	37 3	25 5	+49 2	8 8	59 3	19 2	57 0	18 7
Group C	−26 4	15 4	51 0	28 9	+48 9	8 3	58 7	22 1	63 9	18 4
Total	−27 6	16 4	39 3	28 1	+49 3	8 5	56 6	18 6	57 7	18 5
ΔC A	+2 0		+17 1		−0 8		+5 6		+10 1	
t	1 10		5 06		0 78		2 30		5 36	
p	0 05		0 001		0 05		0 05		0 001	

Differences of the means between Groups A and C (ΔC-A) and their significances as evaluated by the t test.
A Under 140 90 mm. Hg blood pressure
B 140/90–159/94 mm Hg blood pressure.
C 160/95 199/109 mm Hg blood pressure

160/95 mm Hg speaks in favor of a summation effect of elevated blood pressure and obesity But it must be noted that relative body weight is a rather poor index for obesity In general our results of the effects of relative body weight are in agreement with those of Simonson and Keys

It may be of particular interest that the normal age trend [ ] toward a more horizontal heart position is found only in groups with elevated blood pressure (over 140/90 mm Hg) Furthermore differences according to blood pressure in the angle between QRS and T vectors (dA) and in the ratio of R and T amplitude are in a direction opposite to those found in subjects with sustained high levels of physical activity [ ]

Whatever the mechanism asymptomatic elevation of blood pressure is related to manifest ECG and vectorcardiographic differences of statistical and very likely of biological significance The differences are in the direction of those electrical features associated with myocardial hypertrophy and ischemia and are probably the first manifestation of the effect of ventricular myocardial work against an increased head of arterial pressure

Summary

ECG amplitudes and mean spatial vectors are analyzed according to levels of blood pressure in three blood pressure groupings among a sample of putatively healthy laborers who ranged in age from 20 to 60 years (Group A—under 140/90 mm Hg blood pressure Group B—140/90 to 159/94 mm Hg blood pressure and Group C—160/95 to 199/109 mm Hg blood pressure)

the groups with asymptomatic

ate elevation of blood pressure significant differences from the normotensives are found with lower T wave amplitude greater elevation of QRS and T vectors and a widened spatial angle between QRS and T vectors The differences are not due principally to the effect of overweight The normal age trend toward a horizontal electrical heart position is *not* apparent in the normotensive group The ECG and vectorial differences found are in the direction of those electrical features which characterize myocardial hypertrophy and ischemia and they probably represent the earliest ECG signs of the myocardial effect of an increased cardiac work load

The suggestions and criticism of Professor Ernst Simonson of the Laboratory of Physiological Hygiene are appreciated

REFERENCES

1 Selzer A Ebnother C C Packard P Stone A O and Quinn J E Reliability of electrocardiographic diagnosis of left ventricular hypertrophy Circulation 17 255 1958
2 Sokolow M and Lyon T P The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads Am Heart J 37 161 1949
3 World Health Organization Technical Report Series No 168 1959 First report of the expert committee on cardiovascular diseases and hypertension
4 Simonson E A spatial vector analyzer for the conventional electrocardiogram Circulation 7 403 1953
5 Libretti A and Zanchetti A Spatial patterns of ventricular repolarization in arterial hypertension Am Heart J 59 40 1960
6 Rautaharju P M Karvonen M J and Keys A Mean spatial QRS and T vectors in 468 healthy Finnish men aged 20 to 59 years Acta med scandinav (In press)
7 Simonson E and Keys A Effect of age on mean spatial QRS and T vectors Circulation 14 100 1956
8 Simonson E and Keys A The spatial QRS and T vectors in 178 normal middle aged men Circulation 9 105 1954
9 Rautaharju P M Voltage changes in the electrocardiogram as caused by vigorous training Abstracts of Communications III World Congress of Cardiology Brussel 1958 p 411
10 Rautaharju P M and Karvonen M J The effect of heavy work on the magnitude and orientation of the mean QRS and T vectors (To be published)

Left heart volumes in coarctation of the aorta

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Angiocardiography has been used in estimating chamber volumes of the left atrium and ventricle in experimental animals[1,2] and in patients.[3] This report presents some estimates of left atrial and left ventricular volumes in coarctation of the aorta which were made with the use of the technique of Arvidsson. These observations suggest that in cases of coarctation of the aorta without evidence of cardiac failure (1) ventricular ejection is efficient, leaving a small residual volume (30 per cent of end diastolic volume), (2) changes of left atrial volume during a cardiac cycle are small in comparison with those of the ventricle, and (3) findings in repeat studies made after surgical repair of the coarctation do not differ significantly from preoperative values.

Material and methods

Seven patients with coarctation of the aorta were studied at the Children's Clinic of the Karolinska Sjukhuset. In three cases both preoperative and postoperative angiocardiograms were available for study, making 10 studies in all. The vital statistics for each patient are given in Table I.

Children who were less than 7 years of age were given basal anesthesia with tribromoethanol (Avertin), and older children received morphine and scopolamine as premedication. During angiocardiography light intravenous barbiturate anesthesia was administered. Succinylcholine (1 mg. per kilogram of body weight) was given intravenously to inhibit respiration; the anesthetist maintained pulmonary ventilation using oxygen. Just before injection of contrast the lungs were inflated gently with pressure of no more than 10 cm. of water in the face mask. Acetrizoate (Urokon) 70 per cent in a dose of 1.2 ml. per kilogram of body weight was the contrast material used in seven investigations, and diatrizoate methylglucamine (Urografin) 76 per cent in a dose of 2 ml. per kilogram of body weight was utilized in the other three. The medium was injected into the main pulmonary artery in 1.5 to 2 seconds.

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Table I Estimates of left heart volumes with other physiologic data in 10 studies of seven patients with coarctation of aorta

Case	Status	Age Sex	Height (cm)	Weight (Kg)	Body surface (sq M)	Blood pressure (mm Hg) Arm	Blood pressure (mm Hg) Leg	Pulmonary artery Pressure (mm Hg)	Pulmonary artery O_2 saturation (per cent)	Heart rate (cycles/min)	Estimated heart volumes (ml/sq M body surface) Left atrium† ESV	Left atrium† EDV	Left atrium† SV	Left ventricle* ESV	Left ventricle* EDV	Left ventricle* SV	Left ventricle* ESV/EDV	Cardiac index§ (L/min/M²)
1	Preop	M	116	19 4	0 79	1 0/114	0	34/10	67	151	28	14	14	30	75	45	40	6 8
	Postop	11 M	146	29 2	1 11	155/90	135/83	—	—	146	21	9	12	24	73	19	33	7 1
	Preop	7 M	121	25 0	0 92	120/90	0	26/10	67	108	25	15	10	17	72	55	24	5 9
	Postop	11 M	141	37 7	1 23	115/61	9 /13	—	—	116	30	10	20	27	69	42	39	4 9
3	Preop	7 F	116	20 2	0 82	1 5/75	0	22/9	72	140	30	16	14	17	55	38	31	5 3
	Postop	12 F	14	32 7	1 13	125/93	125/88	—	—	165	32	11	21	21	65	44	32	7 2
4	Preop	5 F	101	13 8	0 62	150/100	110/90	19/7	69	115	25	7	18	15	62	47	24	5 4
5	Preop.	6 F	117	21 5	0 93	130/90	75/0	16/5	83	78	33	17	16	16	75	59	21	4 6
6	Preop	9 M	135	31 5	1 07	150/110	0	26/4	71	145	35	20	15	10	56	46	18	6 6
7	Preop	7 F	120	22 2	0 84	145/60	0	20/8	64	186	24	14	10	13	47	34	28	6 3
Averages											28	13	15	19	65	46	29	

Preoperative blood pressures were measured by the cuff method postoperative by intra-arterial needle
*ESV End-systolic volume EDV End-diastolic volume SV Stroke volume
†For the left atrium these terms refer to the volumes at the end of ventricular systole and of ventricular diastole The stroke volume of the left atrium is the difference between these values and is a reasonable estimate of the maximal change in left atrial volume
§Product of heart rate and left ventricular stroke volume

A program was selected to provide six pictures per second during left heart opacification using a roll film changer of the Grdlund type with simultaneous exposures in the anteroposterior and lateral planes

Requirements for inclusion of patients in this analysis were absence of cardiac irregularities during the angiocardiographic examination and a total of at least 14 pairs of frames in which the left atrium and left ventricle presented clear outlines The sequence under examination therefore included four to eight separate cardiac cycles extending over a period of 2 5 to 4 0 seconds Simultaneous recording of an electrocardiogram with the exposures provided the means whereby each frame could be related to the events of the cardiac cycle The exposure times in this series never exceeded 0 023 second (1/45 second) Outlines of the chambers of the left heart were drawn with an accuracy of ± 1 mm (Figs 1 and 2)

Analysis for estimation of the volumes of the left atrium and the left ventricle was carried out by the method of Arvidsson[8] in which it is assumed that the shapes of the chambers do not differ appreciably from an ellipsoid

The measurements used are readily evident from Fig 1 The volume of the left atrium V_{LA} was calculated from the relation

$$V_{LA} = \frac{a}{f_1} \cdot \frac{b}{f_1} \cdot \frac{c}{f_1} \cdot \frac{4}{3}\pi$$

where a b and c are atrial semiaxes in centimeters and f_1 and f are magnification factors of 1 2 and 1 3 respectively and hence

$$V_{LA} = (a\ b\ c)\ (2\ 24) \qquad \text{(Equation 1)}$$

The volume of the left ventricle V_{LV} was calculated from the equation

$$V = \frac{L}{2} \cdot \frac{B}{2f} \cdot \frac{C}{2f} \cdot \frac{4}{3}\pi$$

where B and C are axes of the ventricle and L the true long axis of the ventricular ellipsoid [8] is equal to

$$L = \sqrt{\left(\frac{D \quad \cos\beta}{f}\right)^2 + \left(\frac{A}{f}\right)^2}$$

The magnification factors f_1 and f are the same as for the atrial estimation and β is the angle formed by the ventricular axis projection in the lateral view with the horizontal plane hence

$$V = (L\ B\ C)\ (0\ 336) \qquad \text{(Equation 2)}$$

Individual estimates of left atrial and left ventricular volumes were plotted against time expressed in fractions of seconds after the R wave of the ECG From these values end diastolic end systolic and stroke volumes were obtained Since direct measurements of cardiac output were not available it was calculated as stroke volume times heart rate

Findings

Mean values for the series are given in Table I The volumes obtained in each case are plotted in the composite Figs 3 and 4 each point representing one frame Of necessity the individual points plotted at nearly the same times were obtained from different cardiac cycles

Although data from several cardiac cycles are condensed into one representative cycle, there is relatively little scatter of individual left ventricular volumes During late systole and late diastole the scatter is minimal The averages for end diastolic end systolic and stroke volumes of the left ventricle were respectively 65 19 and 46 ml per square meter of body surface From the product of left ventricular stroke volumes and heart rates cardiac outputs were calculated Expressed as cardiac indices these values range from 4 6 to 7 2 L /min /M In general the subjects with the highest calculated flow rates had the most rapid heart rates

The changes of volume for the left atrium were much less marked No variation of a magnitude comparable to that of the stroke volume of the ventricle could be detected The atrial volume averaged 28 ml /M at the end of ventricular systole and 13 ml / M during diastole and early systole No consistent presystolic decrease in left atrial volume could be identified

Comment

Accuracy of estimation of volumes In his study of adult patients with mitral disease Arvidsson considered on the basis of mathematical analysis that the maximal error inherent in the application of his method to the determination of left atrial volume was

Table I. Estimates of left heart volumes with other physiologic data in 10 studies of seven patients with coarctation of aorta

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	Postop	13 M	146	29.2	1.11	155/90	135/83	—	—	146	21	9	12	24	73	49	33	7.1
2	Preop	7 M	121	25.0	0.92	120/90	0	26/10	67	108	25	15	10	17	72	55	24	5.9
	Postop	11 M	141	37.7	1.23	135/64	92/73	—	—	116	30	10	20	7	69	47	39	1.9
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	Postop	12 F	142	32.7	1.13	1 5/93	125/98	—	—	165	3	11	21	21	65	44	32	7.2
4	Preop	5 F	101	13.9	0.62	150/100	110/90	19/7	69	115	25	7	18	15	62	47	24	5.4
5	Preop	6 F	117	21.5	0.93	130/90	75/0	16/5	83	78	33	17	16	16	75	59	21	4.6
6	Preop	9 M	135	31.5	1.07	150/110	0	26/4	71	145	35	20	15	10	56	46	18	6.6
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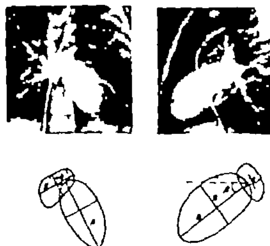


Fig 1 Paired angiocardiograms (posteroa terior and lateral projection) obtained during entricular diastole Calculations of heart olumes are made as described in the text from the dimensions marked on the line drawings below In these the lower case symbol refer to semiaxes and the capital to xes

approximately ±8 per cent No experimental comparisons were available for testing such errors Possible errors due to oblique orientation of the atrium are of an order of magnitude which according to Arvidsson s analysis is to be considered small The shape of the atrium however needs special attention Whereas Arvidsson s investigation was concerned with dilated atria ours was concerned with atria that were probably undistended or only slightly distended (Fig 1) and thus were less regular ellipsoids Consequently the percentage errors in our estimates of volume may have been greater than in his

Our errors of measurement were tested by animal experiments in collaboration with Nordenstrom Three dogs which weighed from 8 to 30 kilograms were taken after other experiments killed and subjected to thoracotomy A glass funnel was tied into the left atrial appendage and through it Wood s metal (melting point 64°C) was poured to fill the left atrium left ventricle and pulmonary veins The thorax then was closed the animal was suspended in a sling and posteroanterior and lateral roentgenograms of the solid radiopaque cast were obtained The cast was removed from the animal the myocardium was dissected free and the portions which filled the pulmonary veins were cut off at their junction with the atrium The volumes of these casts were measured by water displacement and compared with three or four paired roentgenograms on which the outline of the casts were measured by different observers The volumes of the casts measured 21 44 and 82 ml and in all but two instances the estimate based on each film pair agreed within 3 per cent the exceptions being −9 per cent and −6 per cent for the largest heart specimen Separate estimates of atrial and ventricular volumes could not be made

These observations made in dogs and with the use of a high-contrast object support the thesis of Arvidsson[6] and of Gribbe and associates[2] that the geometry of a simple ellipse provides a basis for accurate and practical estimation of the volume of cardiac chambers Theoretical considerations suggest that if errors are present the computed values exceed the actual It should be mentioned that Gribbe[4] has found good agreement in stroke volume as determined by both the direct Fick method and angiocardiography in dogs

During diastole overlap between the

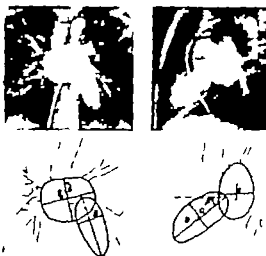


Fig 2 Paired angiocardiograms (posteroa terior and lateral projections) obtained during entricular systole Note the larg dimen ions f the left atri m in the posteroanterior as compared t the lateral projection in rel tion t the change from Fig 1

Dr Bjorn N d strom Ch f of the Roentgen Diagnostic Department Thoracic Karoli ka Sj Hospital

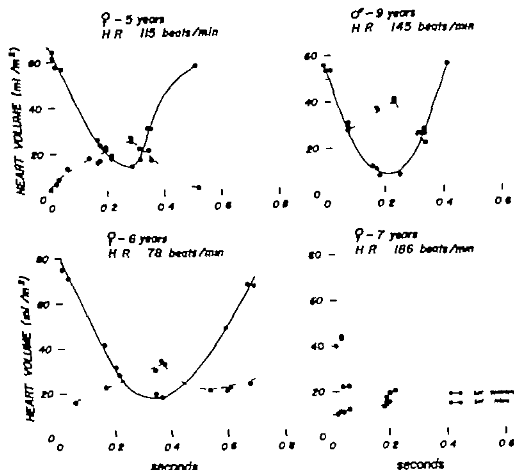


Fig 3 Changing volumes (milliliters per square meter of body surface) of the left ventricle and left atrium in Cases 4 5 6 and 7 The solid lines indicate approximately the continuous volume curves No line has been inscribed in the panel for Case 7 because chance synchronization between the filming rate and heart rate prevented suitable dispersion of the volume estimates

outlines of the left atrium and the left ventricle is obvious In children with coarctation of the aorta however the volume of overlap can be shown by measurement to be of the order of 1 or 2 ml Since this is so small the correction has been neglected in the present study Since the volume of the papillary muscles was thought not to affect the stroke volumes this factor was also neglected In the experiments of Gribbe and associates[8] on dogs the volume of the papillary muscles and the trabeculae carneae was estimated in cast studies No such information was available in the present study

Frames exposed at closely comparable times in different cardiac cycles allowed in our investigation comparison of estimates of volumes based on chamber outlines of widely different contrast Although the frames obtained early in the sequence were of much higher contrast than those obtained later there was no systematic difference between the volumes calculated from early and late exposures

Opacification of the left heart was discernible in an average of seven cardiac cycles (range 6 to 14) This would tend to minimize the potential effect of the addition of the injected volume of contrast on the size of the left heart The addition of such a substantial volume however would be to increase the apparent volume of fluid passing through the chambers of the left heart by approximately 10 per cent

Physiologic considerations An approach to the determination of the efficiency of left ventricular ejection can be made by considering the volume of blood left at the end of systole (Table I) If preoperative and

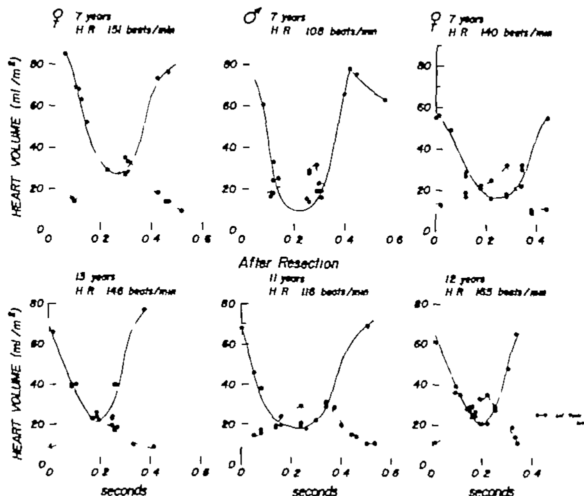


Fig. 4. Changing volumes (milliliters per square meter of body surface) of the left atrium and left ventricle preoperatively (*above*) and 4 to 5 years postoperatively (*below*) in Cases 1, 2, and 3. Note the general similarity in the magnitude and changes in volumes obtained in the paired studies.

postoperative studies are counted separately, our investigation affords 10 estimates of residual volume in the left ventricle. The values range from 10 to 30 ml./M.², averaging 29 per cent of the end-diastolic ventricular volume. This implies highly efficient ejection.

These results are in relatively good accord with the data that have been presented by Gribbe and associates.[8] These investigators, using cineangiocardiographic recordings from anesthetized dogs, calculated the average stroke volume to be 60 per cent of the end-diastolic volume, implying an average residual volume of 40 per cent. Their findings in nonanesthetized dogs were similar.

These end-systolic volumes are considerably lower than those reported by Chapman and associates[1] and by Holt.[9] In a cineangiocardiographic study of anesthetized dogs, Chapman's group found that the residual volume of the left ventricle averaged 51 per cent (range, 37 to 56 per cent) of the end-diastolic volume. Holt, using dye dilution and electrical conductivity methods in dogs, reported that residual volumes averaged 54 per cent of end-diastolic values. Chapman and co-workers had reported previously, however, a cineangiocardiographic study on one healthy human subject in whom they found the residual volume to be 15 per cent of the end-diastolic volume.

It is possible that the patients in our study had lighter anesthesia and better oxygenation of their tissues than did the anesthetized dog. These two factors may be of importance in obtaining low end-systolic values. Neither the contrast me-

dium nor the slightly elevated intrabronchial pressure (5 to 10 cm of water) are thought to have affected greatly the left heart volumes in our subjects. It is frequently observed, however, that the heart rate increases with the introduction of anesthesia. No further change in heart rate occurs during angiocardiography, although bradycardia may develop some while after the time of the left heart opacification.

Left ventricular stroke volumes in our 10 studies ranged from 34 to 59 ml./M.². Such values are reasonable and are of the order of magnitude one might expect in normal subjects. However, the estimated cardiac indices were rather high. If 5.5 L./min./M.² is taken as the upper limit of normal values for children, only four of the 10 were within the range of normal. The heart rates of the patients with the higher cardiac indices ranged from 108 to 186.

One patient, the last in Table I, had such a high heart rate that the frames (six exposures per second) happened to fall in only two phases of the cardiac cycle. All points clustered about the lines representing 0.04 and 0.20 second after the R wave, and hence no curve could be constructed as was easily done in the other cases. This case illustrates the shortcomings of this method of estimation of volume when the heart rate is very rapid.

The changes of atrial volume, as estimated by this method, are remarkably reproducible, and when plotted they form a curve which is in many ways the inverse of that obtained from the ventricle. However, the magnitude of the change of atrial volume averages only one third that of ventricular volume. Arvidsson[4] has suggested the reason for this, namely, the atrium is a chamber closed only at one end for a relatively short time during any cardiac cycle and hence during diastole the atrium does not expand because inflow and outflow occur simultaneously.

These findings indicate that the passage of the greater proportion of the stroke volume into the left ventricle is governed by factors other than atrial contraction. Indeed, the greatest change in atrial volume appeared to occur immediately after systole and not in presystole, although the rapid heart rates render such distinctions uncertain.

Effect of surgical repair. Three patients were studied before and up to 5 years after surgical repair of coarctation. Each repair was considered adequate by the surgeon and comparison of preoperative and postoperative blood pressures in the arms and legs supports the surgeon's opinion. No significant changes were demonstrated in any of the parameters studied: left atrial end-systolic and end-diastolic volume and left ventricular end-systolic and end-diastolic volume.

The fact that the preoperative and postoperative studies agreed closely suggests that left ventricular volumes were within the range of normal in these children before operation. A definitive opinion should await the results of simultaneous determination of the cardiac output according to established physiologic method.

Summary

Arvidsson's method of estimating volumes of the left heart chambers by angiocardiographic techniques has been found to be practical in application. The method has been applied in 10 studies of seven patients with compensated coarctation of the aorta. Left ventricular stroke volumes were found to average 46 ml./M.² (range, 34 to 59) and the end-systolic volume in the left ventricle to average 19 ml./M.² (range, 10 to 30). This evidence indicates that left ventricular ejection is highly efficient.

Changes in left atrial stroke volume were much less marked, averaging only 15 ml./M.² (range, 10 to 21) during any cardiac cycle.

No significant differences in changes of left heart volume were found in three patients who were studied both before and 4 to 5 years after surgical correction of the coarctation.

REFERENCES

1. Chapman, C. B., Baker, O., and Mitchell, J. H.: Left ventricular function at rest and during exercise, J. Clin. Invest. 38:1202, 1959.
2. Chapman, C. B., Baker, O., Reynolds, J., and Bonte, F. J.: Use of biplane cinefluorography for measurement of ventricular volume, Circulation 18:1105, 1958.
3. Gribbe, P., Hirvonen, L., Lind, J., and Wegelius, C.: Cineangiocardiographic recordings of the cyclic changes in volume of the left ventricle, Cardiologia 34:348, 1959.
4. Gribbe, P.: Comparison of the angiocardiographic and the direct Fick methods in de-

termining cardiac output Cardiologia 36:20 1960

5 Holt J P Estimation of the residual volume of the ventricle of the dog heart by two indicator dilution technics Circulation Res 4 187 1956

6 Arvidsson H Angiocardiographic observations in mitral disease with special reference to volume variations in the left atrium Acta radiol Suppl 158 11 1958

Blood pressure measurements of urban Zulu adults

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Various observers have differed widely in their reports on blood pressure measurements and the prevalence of hypertension among Africans. As Phillips and Burch[1] stated in a recent review article, "some reports show that native Africans have lower arterial blood pressure than Caucasians and that hypertension is rare in the Negro,[2] whereas others report hypertension not to be rare in Native Africans but that it may even be more frequent than in Caucasians."

The present study was part of a larger project on nutrition and hypertension begun in 1958 by the Department of Social, Preventive and Family Medicine, University of Natal.

Subjects and method

The study was carried out in an African housing scheme occupied predominantly by Zulus (72.5 per cent). The persons examined comprised 382 adults (271 women and 111 men, aged 18 years or more) drawn from a randomly selected sample consisting of all the adult Zulu residents of every seventh home in the housing scheme. Of the initial sample, 76.6 per cent of the women and 45.2 per cent of the men were examined. The others could not be examined for a variety of reasons, so that there was some question as to how representative the sample was. Accordingly, visits were made to the homes of half of the persons who had not been examined in order to ascertain the reasons for their nonexamination and, more important, to see whether they differed from examined persons in their marital state, parity, social class, father's social class, income, food expenditure, education, and other variables. Since the few differences which were found were slight or involved factors bearing no significant relationship to levels of blood pressure, it was concluded that the persons examined were fairly representative of the total Zulu population of the housing scheme. Men in the lowest social class (unskilled laborers), for example, were significantly underrepresented among the per-

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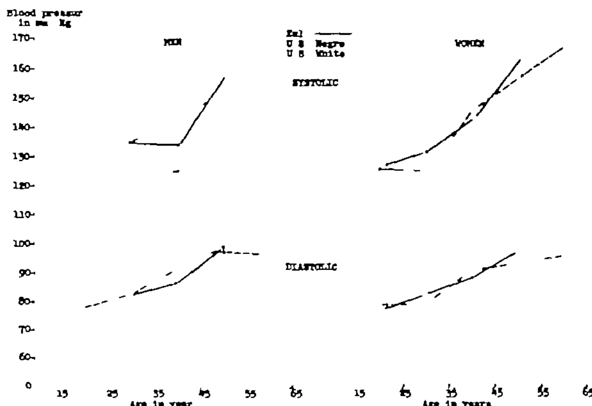


Fig 1 Mean systolic and diastolic blood pressures of Zulu adults by sex and age Comparison with Negro and white adults in the United States [illegible] The values charted for Zulu adults are based on [illegible] available measurements for persons aged 18-64 (including pregnant women) excepting men aged 18 24 and 55 64 who numbered 14 and 8 respectively

sons examined Although social class was found to bear a significant relationship to the levels of blood pressure standardization of the results in accordance with the social class structure of the total sample produced a negligible difference in the prevalence of hypertension

Blood pressures were taken in the Institute of Family and Community Health Durban to which participants were transported from their homes This Institute is adjacent to the housing scheme for which it has provided a medical service for some years and most of the subjects were familiar with it All the readings were made by the same physician (C S) with the exception of three cases Patients were seated and the pressure was taken with a Baumanometer the diastolic pressure being equated with the disappearance of the sound In order to examine the variation of blood pressure in the two arms [12] the initial reading of blood pressure was taken on the right in some cases and on the left in others For the purposes of the analysis which follows the initial reading was used regardless of whether it was taken on the left or the right side

Two separate criteria were used in classifying persons as hypertensive the first being more stringent criterion *a*—a systolic pressure of over 160 mm Hg and/or a diastolic pressure of over 96 mm Hg criterion *b*—a systolic pressure of 140 mm Hg or more and/or a diastolic pressure of 90 mm Hg or more

The sample included 5 persons with congestive cardiac failure all ambulant 4 of them were hypertensive

Results

The levels of mean and median blood pressure of our subjects are set out in Table I and the prevalance of hypertension using the two separate criteria explained above is shown in Table II

Studies of hypertensive women of the United States [14] and of African women [15] have indicated that blood pressures tend to drop in pregnancy This was confirmed

in our subjects Of the 31 pregnant women who were 20 to 34 years of age none were hypertensive by criterion *a* and 16 1 per cent by criterion *b* Of the other 108 women in this age group 19 4 per cent were hypertensive by criterion *a* and 38 9 per cent by criterion *b* The difference was significant (p < 01 using criterion *a* and < 05 using criterion *b*) The mean ages of the pregnant and nonpregnant women were similar 31 5 and 30 4 years respectively In view of this finding separate figures for nonpregnant women are given in Table I and data relating to pregnant women are not included in the analysis of the prevalence of hypertension (Table II)

Table I Blood p essure (mm Hg) of Durban Zulu adults by sex and age Medians means and standard deviations

Sex nd ge (yr)	N mber	Systolic pressure			Diastolic pressure		
		Median	Mean	Standard deviation	Median	Mean	Standard deviation
Men							
18– 4	14	139	136	—	84	81	—
25–34	34	138	133	17 25	80	81	13 63
35–44	32	131	133	18 14	84	84	10 57
45–64	22	156	157	26 18	95	98	12 19
65 nd over	9	1 0	171	—	90	90	—
	111						
Women							
18–24							
Total group	56	128	127	16 46	78	77	13 95
Nonpregnant women	45	129	129	15 82	79	80	20 15
25–34							
Total group	100	128	131	20 35	80	82	16 06
Nonpregnant women	80	130	134	16 94	84	84	25 15
35–44	59	141	144	28 10	90	88	14 44
45–64	43	160	165	28 57	100	98	15 04
65 and over	11	175	165	—	88	87	—
	271						

*There were no pr gnant women in these ag gr ups
Sta dard deviation are not given for gr ups which contained f wer than 20 persons.

Table II P evalence per cent of hypertension by sex and age

Age (y)	Percentage with hypertension					
	Men			Women		
	N mber	Criterion *a*	Criterion *b*	Number	Criterion *a*	Criterion *b*
18– 4	14	28 6	50 0	45	6 7 } §	31 1
25–34	34	17 6	50 0	80	23 8 }	42 5 } ‡
35–44	37	1 6 } †	43 8 } †	39	35 6 } †	64 4 }
45 or over	31	58 1 }	80 6 }	56	6 3 }	5 0
45–54	15	60 0	80 0	25	60 0	3 0
55–64		37 1	71 4	20	65 0	80 0
65 or over	9	55 6	88 9	11	63 6	72 7

A defi ed by the two criteria explai ed in the xt
†p 05
‡p
§ 01
Pregna wom were excl ded f m thi analysis

In both sexes levels of mean blood pressure and the prevalence of hypertension rose with age This increase becomes apparent after the age of 44 in men but sooner in women (Tables I and II) This earlier rise in women was reflected in the finding that in the 35-44 year age group the women had a higher mean and median systolic blood pressure and a greater prevalence of hypertension than did the men The difference in mean systolic pressures is statistically significant ($p < .05$)

The mean systolic and diastolic pressures of our subjects are shown graphically in Fig 1 by age and sex together with comparative figures for population samples of Negro and white persons in Georgia U S A[14]

Discussion

It is apparent from Fig 1 that our subjects tend to have mean pressures similar to those of Negroes of the United States who are recognized as having a high prevalence of hypertension[1] and higher mean pressures than those of whites of the United States Excepting the diastolic pressures of men who are 25 to 44 years of age the mean pressures are closer to those of the Negro group cited than to those of the white group

The conclusion that this urban Zulu group shows a relatively high prevalence of hypertension is supported by data on a similar group of Zulus living in a rural native reserve In general the urban Zulus have a significantly higher incidence of hypertension and significantly higher blood pressure values[9]

The evidence suggesting an earlier rise in blood pressure in women than in men is consistent with Schrire's findings among Coloured hospital patients in Cape Town[17] and those of Fraser among Coloured and African hospital patients in Johannesburg[18]

Summary

A study of a population sample of urban Zulu adults in Durban South Africa revealed a high prevalence of hypertension Mean blood pressures tended to be similar to those of Negroes of the United States and higher than those of whites of the United States

In both sexes levels of mean blood pressure rose with age this rise appeared earlier in women than in men

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REFERENCES

1 Phillips J H and Burch G E Cardiovascular diseases in the white and Negro races Am J M Sc 238 97 1959
2 Donnison C P Blood pressure in the African native Lancet 1 6 1929
3 Jex Blake A J Primary arterial hypotension East African M J 13 34 1936
4 Krober F Beobachtungen und Erfahrungen in der ostafrikanischen Praxis Klin Wchnschr 12 724 1933
5 Shattuck G C The African republic of Liberia and the Belgian Congo Report of the Harvard Expedition to Liberia Cambridge 1930 Harvard University Press
6 Vint F W Postmortem findings in the natives of Kenya East African M J 13 332 1937
7 Williams A W Heart disease in the native population of Uganda East African M J 21 328 1944
8 Becker B J P Cardiovascular disease in the Bantu and coloured races of South Africa I Incidence pathology and general features South African J M Sc 11 1 1946
9 Becker B J P Cardiovascular disease in the Bantu and coloured races of South Africa V Hypertensive heart disease South African J M Sc 11 107 1946
10 Heimann H L Strachan A S and Heymann S C Cardiac disease among South African non Europeans Preliminary note Brit M J 1 344 1929
11 Ordman B A review of the incidence of hypertension in the non European races Survey of blood pressures in the South African Bantu Clin Proc 7 183 1948
12 Uys C J The pathology of renal disease in the Bantu on the Witwatersrand Hypertensive vascular disease South African J Lab & Clin Med 2 13 1956
13 Slome C Scotch N Abramson J H and Gampel B Variations in blood pressure in the two arms of urban Africans Am Heart J 58 41 1959
14 Chesley L C Annitto J E and Jarvis D G Interaction of pregnancy and hypertensive disease Am J Obst & Gynec 53 851 1947
15 Comstock B W An epidemiologic study of blood pressure levels in a biracial community

in the southern United States Am J H giene 6 771 19 7
16 Scotch N A A preliminary eport on the relation of sociocultur l factors to h pertension among the Zulu Ann New York Acad Sc (I press)
17 Schrire V The racial incidence of heart disease at Groote Schuu Hospital Capetown Part II H perten ion and vascular disease of the heart Am HEART J 56 42 1958
18 Fraser B N Manifestation and aetiology of hyperten ion in the Coloured and Ba tu Brit M J 1 61 1959

Heart murmurs simulated by arterial bruits in the neck

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The proper assessment of systolic murmurs in children is a common problem in all cardiac clinics. Although physicians are now generally alert to the frequency of physiologic murmurs in children, many such murmurs nevertheless fall into the borderline category and are referred for further cardiac evaluation.

This communication reviews one uncommon type of physiologic murmur in children in which a systolic arterial bruit arising in the lower neck is transmitted to the base of the heart and recorded during routine physical examination as an aortic and/or pulmonic systolic murmur. In some instances the bruit comprises most or all of the basal murmur; in other cases the bruit augments an innocent cardiac murmur so that Grade 3 or more intensity results from the dual source of sound.

Four patients with supraclavicular bruits are reported herein who presented basal systolic murmurs which could be well heard along the upper sternal borders. In Cases 1 and 2, transmission was prominent enough to the right of the sternum that an aortic ejection murmur was simulated. In Cases 3 and 4, the maximum intensity of the transmitted bruit was along the left sternal border simulating a pulmonary ejection murmur. The illustrated phonocardiograms were recorded with Sanborn Twin Beam or Stethocardiette phonocardiograph at a paper speed of 75 mm. per second. The microphone was held by the hand over the neck with just enough pressure to provide good contact with the surface of the skin.

Case reports

Case 1. A 7-year-old asymptomatic boy was referred to the rheumatic fever clinic for evaluation of a cardiac murmur which was known to have been present since he was 3 years old. Penicillin prophylaxis had been started when this murmur was discovered and had been *discontinued only recently.* Frequent syncopal episodes which were found to be petit mal were controlled with medication. There was no history of rheumatic fever. Family and past medical histories were normal. Examination disclosed a Grade 3 ejection type of systolic murmur which was heard best in the pulmonic area but also along the mid left sternal border and in the aortic area (Fig. 1). Prominence of the aortic murmur was in particular the auscultatory feature which raised the question of aortic stenosis. Inching the stethoscope up the sternal borders revealed loud bilateral supraclavicular bruits. A physiologic third sound and a venous hum were prominent. The ECG and chest x-ray film were normal.

Case 2. A 9-year-old Negro boy was admitted to the hospital with acute glomerulonephritis. An aortic ejection type of systolic murmur was discovered as an incidental finding on physical examination and was regarded as indicating aortic stenosis until the significance of his loud right supraclavicular bruit was appreciated (Fig. 2). The ECG and chest x-ray film were normal.

Case 3. A 14-year-old asymptomatic school boy was referred for evaluation of a cardiac murmur. Systemic review and past medical and family histories were normal. Examination disclosed a tall asthenic white boy with slight pigeon breast and prominent point of maximal impulse. A Grade 3 systolic murmur was present in the pulmonary area with transmission down the left sternal border to the apex. Inching the stethoscope up the left sternal

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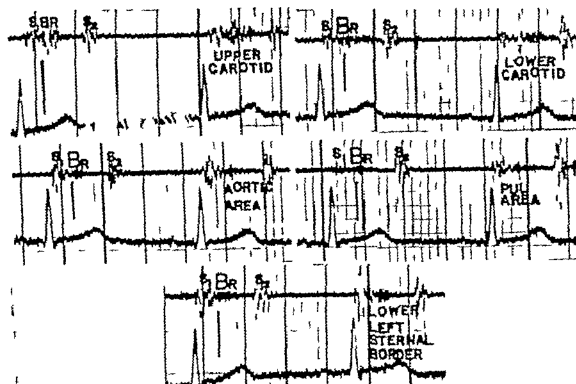


Fig 1 Asymptomatic 7 year-old boy with prominent basal systolic murmurs which correspond to louder supraclavicular bruits

border from the pulmonic area disclosed that the murmur progressively increased reaching its peak intensity just above the medial clavicle on both sides (Fig 3) A venous hum and prominent physiologic third sound were present. The ECG and chest x ray film were normal

Case 4 A 17 year old white asymptomatic x ray technician was referred for evaluation of cardiac murmur Past medical and family histories were normal A Grade 3 ejection type of systolic murmur was evident in the pulmonic area and was also heard in the aortic area and at the apex. Inching the stethoscope up the sternal borders disclosed loud supraclavicular bruits bilaterally (Fig 4) Examination also disclosed a thrusting point of maximal impulse prominent physiologic third sound and venous hum The ECG and chest x ray film were normal

Discussion

The bruit is characteristically abrupt occupying in all no more than a third of systole The onset is later than that of basal ejection murmurs commencing usually 0 12 to 0 16 second after the onset of QRS It exhibits a diamond shaped contour with swift development of Grade 3 to 4 peak intensity and prompt decline around mid systole Such a contour classifies the murmur as ejection in type the early onset and brief duration suggest a flow rather than obstruction mechanism It is best heard immediately above the clavicle(s) and fades out rapidly as the stethoscope is inched along the common carotid or subclavian arteries It is less well heard below the clavicles and ordinarily makes insignificant contribution to the basal cardiac sounds However as illustrated here bruits of exaggerated intensity may be transmitted to the aortic or pulmonic regions The murmurs are sometimes bilateral but tend to predominate on one side or the other Carotid or subclavian compression has no significant effect likewise no change occurs with various postural maneuvers

Edwards and Levine[1] have called attention to the impact sound in early systole which precedes a crescendo decrescendo bruit when an artery is partially compressed This sound is clearly identified in Figs 2 3 and 5 indeed on superficial inspection the impact sound could be mistaken for the first heart sound

The mechanism of these bruits is speculative Obstruction is a well known cause of murmurs over vessels Mild narrow

causes a short systolic bruit; more severe degrees of occlusion prolong this murmur so that in marked obstruction a continuous murmur may be heard over the stenotic segment. The bruits described here are all short, early systolic, indicating that any obstruction present is probably mild. The other features of hypercirculation which are present (thrusting point of maximal impulse, prominent ventricular rapid filling sound, venous hum) suggest a flow mechanism. *Possibly these murmurs arise* from the aortic arch, where streams of blood enter the great branches at high velocity. The great vessel orifices might be relatively narrow in early systole when large increments of flow develop abruptly after the onset of ventricular contraction. The impact sound which is sometimes present suggests sudden distention of the vessels. Failure of subclavian or carotid compression to obliterate these bruits points to an origin proximal to the cervical segments of these vessels. Since the subjects were healthy young persons, a physiologic origin appears likely; since angiographic studies were not justified, etiologic considerations are necessarily tentative.

That these bruits arise from the proximal segments of branches of the aortic arch was strongly suggested by the findings in a 48-year-old man who was admitted because of recent dysarthria and hemihyperesthesia. Examination disclosed a loud systolic bruit in the right medial supraclavicular region (Fig. 5) which was identical in timing and location to the bruits described above in young healthy individuals. This murmur could be readily followed down to the aortic area, where it *simulated an aortic ejection* murmur. Like the physiologic bruits, it faded out rapidly when the stethoscope was inched up the common carotid, and was not significantly altered by subclavian or carotid compression. Because of hypertension in the right upper extremity and hypotension in the left upper extremity, as well as the bruit, the aortic arch was explored. A prominent thrill was palpated over a narrowed sclerotic proximal innominate artery. The degree of obstruction was not severe and surgical intervention was withheld. Thromboendarterectomy was performed on a severely narrowed proximal left subclavian artery.

That cervical bruits transmit to the pre

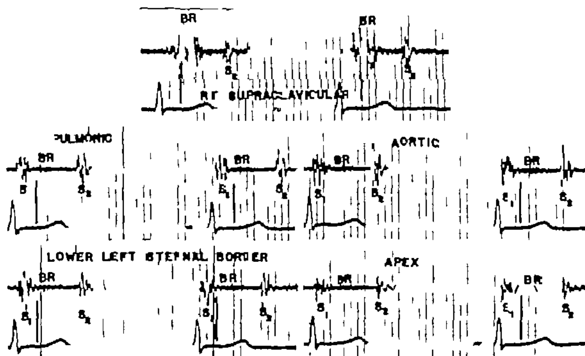


Fig. 2. Nine-year-old Negro with acute glomerulonephritis. Loud right supraclavicular bruit (*BR*) transmits to base of heart, simulating aortic stenosis. Normal ECG and x-ray film. Note impact sound (I) in supraclavicular region.

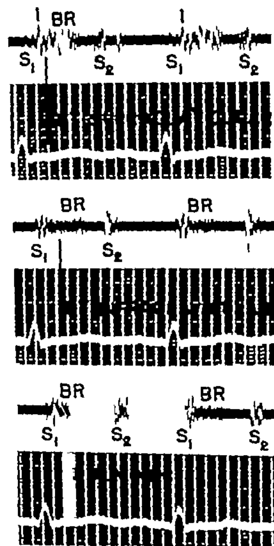


Fig 3 Fourteen year-old asymptomatic boy with Grade 3 pulmonic systolic murmur derived from loud supraclavicular bruit (BR) Note impact sound (') in supraclavicular region

cordium has been previously emphasized by Cassels Levine and Harvey and others Similarly confusing transmission of venous hums has also been described It is not possible to state the relative frequency of this mechanism of functional basal cardiac murmurs as compared to true aortic and pulmonic ejection murmurs It is our impression that although the majority of physiologic basal murmurs are not on this basis cervical bruits will be found to occasionally contribute to such murmurs if auscultation of the neck is regularly practiced Since bruits arise from the compression of normal vessel vascular auscultation should be done gently so as not to create external pressure with the stethoscope piece

Occasionally the murmur of aortic stenosis is loudest in the supraclavicular region These instances occur in older patients with emphysema or other thoracic deformities and are not found in the young patient with normal lungs and chest structure Thus this differentiation has not been a factor in the patients discussed (Fig 6)

The clinical significance of this phenomenon lies in the fact that all patients reported upon here were referred because of the possibility that they had heart disease Indeed one patient was examined several times in a cardiac clinic before supraclavicular auscultation disclosed the basis of his murmur Aortic systolic mur

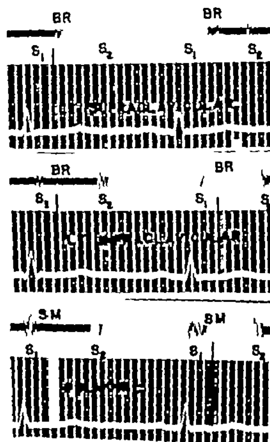


Fig 4 Seventeen year old with Grade 3 pulmonic systolic murmur Loud supraclavicular bruit transmitted down to sternal border to area of pulmonic systolic pulmonic murmur Grade 3 attributed to distal source of murmur

murs are less frequently encountered in children than are murmurs to the left of the sternum Thus an aortic systolic ejection murmur in the intensity range of Grade 2 to 3 seriously raises the question of aortic stenosis This lesion when mild may be manifested solely by such a murmur Since left heart catheterization in the child is a formidable and sometimes inconclusive undertaking the cause of such murmurs is often left undetermined rather than attempt this procedure In like fashion Grade 2 to 3 pulmonary systolic murmurs in the absence of other findings are often of uncertain explanation Catheterization and angiocardiography are considered not to be justified for these borderline murmurs when the remaining clinical data are benign Transmitted arterial bruit should be considered in all young patients who present a prominent basal systolic murmur without other evidence of heart disease Other evidences of rapid circulation and slender chest configuration should increase suspicion

Summary

1 A systolic ejection type of bruit is sometimes heard in the medial supraclavicular regions of healthy young persons

2 This bruit, when prominent, may transmit to the basal region of the heart and either simulate a systolic murmur or augment one already present

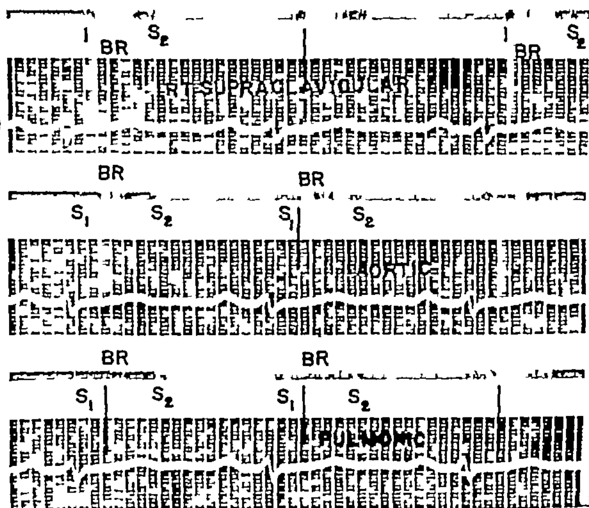


Fig 5 Forty-eight year-old man with right supraclavicular bruit (*BR*) which transmits well to the aortic area and fades out in the pulmonic area. Atherosclerotic narrowing and thrill at innominate artery orifice demonstrated by operation Note impact sound (I)

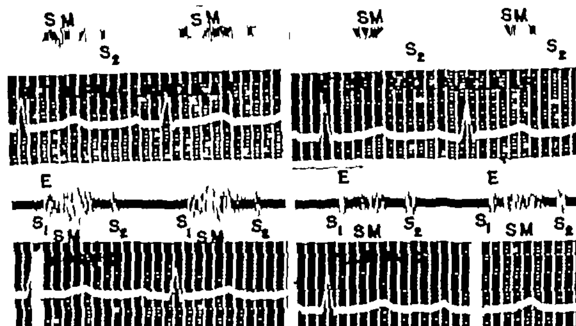


Fig 6 Fi year-old girl with congenital aortic stenosis Note that the loud aortic murmur is softer in the supraclavicular region in contrast to the bruits illustrated Recordings were made with the same volume setting in each region E Aortic ejection sound

3 At times the systolic murmur so produced may be Grade 3 in intensity and simulate an organic murmur

4 Persons who exhibit this phenomenon are often of slender body build and have ventricular rapid filling sounds vigorous apical impulse and venous hum

REFERENCES

1 Edwards E A and Levine H Peripheral vascular murmurs A M A Arch Int Med 90 284 1952
2 Myers J D Murdough H V McIntosh H D and Blaisdell R K Observations on continuous murmurs over partially obstructed arteries A M A Arch Int Med 97 726 1956
3 Murdough H V J and McIntosh H D Continuous arterial bruit as an index of collateral blood pply New England J Med 259 11 0 1958
4 Crevasse L and Logue R B Carotid artery murmurs J A M A 167 177 1958
5 Cassels D E Symposium on cardiovascular disease diagnosis of rheumatic fever Pediat Clin North America 1 231 1954
6 Levine S A and Harvey W P Clinical auscultation of the heart ed 2 Philadelphia 1959 W B Saunders Company p 376

The effects of "dry" heat on the circulation of man
General hemodynamics in patients with chronic pulmonary emphysema

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Data presented by us in a previous report delineated the general hemodynamic effects of the exposure of resting patients with enlarged left ventricles, compensated and in failure, to a dry ambient environment of 98° ± 1 and 40 per cent humidity ±3 for a period of 2 hours. This exposure resulted in a significant fall in the pressures of the pulmonary and peripheral arterial beds with a decrease in the respectively calculated resistances; no change occurred in the oxygen consumption and the cardiac output. The calculated work of the left ventricle decreased. It was speculated that the short-term exposure to a warm dry environment was not deleterious to these patients, although Burch[a] has repeatedly emphasized the ill effects of a *hot and humid* environment upon such individuals.

It is a common clinical observation that people suffering from chronic pulmonary disease are also poorly tolerant of hot and humid weather. Contrariwise, it appears important to know whether these people tolerate a warm and dry environment, at least in the resting state and for a brief period of time, as well as people with a diseased left ventricle[1] would appear to do. The current report presents the data gathered in 10 patients with chronic pulmonary emphysema who were subjected for 2 hours to an ambient temperature of 98° F. and a humidity of 40 per cent.

Materials and methods

Ten male patients who ranged in age from 39 to 63 years were studied. All had chronic pulmonary emphysema of varying severity, as gauged in all instances by a decreased total vital capacity, a reduction of the first second expiration time to less than 60 per cent, and increases in the total lung volume and residual functional volume to levels above 40 per cent of the predicted normal values. None of the patients had a demonstrable diseased left ventricle, and all were normotensive.

The details of procedure were identical to those previously reported for the patients with diseased left ventricles.[1] All studies were performed in the postabsorptive state, but in most instances small doses of chloral hydrate rather than a barbiturate were employed for sedation. After right-sided cardiac catheterization

With the technical assistance of Gladys [illegible], R.N., [illegible] Jason [illegible], R.N., and [illegible], A.B.
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Table I Individual data for 10 subject with chronic pulmonary emphysema (control levels and changes after ? hour exposure to ambient temperature of 95° ± 1° ?)

Patient—Race Sex Age Body Surface		P	Pa	?	?	HR	?/M²	BMRO₂/M	? ? D	C I	pCO	? Hb	? TR	PTR	Peripheral arterial sat (%) ( )
C A 62 W M 1 (0	C	(3 7)	(9 6)	17/11 (13)	116/69 (90)	65	1 42	96	4 99	1 91	34	1 62	336	2 301	90 2
	2	(3 9)	(9 9)	18/11 (14)	102/(5 (9)	81	5 51	130	5 44	2 39	2(	2 05	293	1 652	8) 8
J B 61 W M 1 67	C	(2 3)	(12 1)	31/1 (19)	11 /67 (84)	73	4 25	104	5 48	1 91	3)	2 67	482	2 100	90 4
	2	(2 2)	(1 3)	2)/14 (1))	95/55 (69)	75	4 35	110	5 65	1 90	33	74	477	1 659	89 7
J McC 59 W M 1 47	C	(– 4)	(14 2)	37/ 1 (8)	103/75 (89)	93	3 70	95	6 93	1 27	3)	65	1 198	3 763	91 2
	2	(– 9)	(14 1)	34/21 (27)	)2/70 (82)	101	3 79	107	7 (4	1 39	40	85	1 056	3 209	91 1
C F 51 W M 2 01	C	(5 7)	(18 2)	43/16 (27)	111/78 (100)	79	3 90	130	4 83	70	15	4 82	395	1 163	97 1
	2	(5 0)	(20 1)	40/ 1 (30)	123/72 (91)	9(	4 59	131	4 70	2 90	41	(01	421	1 283	96 7
I S 19 W M 1 6)	C	(4 6)	(26 2)	32/17 (4)	115/77 (90)	(9	3 31	103	4 51	2 25	52	7 01	199	1 992	98 1
	2	(4 5)	(7 1)	31/18 (4)	111/74 (90)	74	4 40	126	4 36	97	46	7 32	306	1 484	96 5
J D 44 N M 1 92	C	(3 0)	(11 5)	29/13 (19)	106/72 (92)	(7	6 85	85	5 00	1 0	45	2 06	49	2 195	92 5
	2	(–2 0)	(5 2)	23/10 (15)	80/54 (63)	75	8 20	111	5 31	2 10	37	2 16	313	1 315	91 4
H I 39 N M 1 86	C	(1 0)	(19 0)	57/29 (34)	154/80 (101)	68	76	97	4 54	16	56	5 55	675	071	89 4
	2	(1 4)	(18 0)	54/23 (32)	127/78 (90)	0	3 02	130	4 79	2 71	5)	6 12	507	1 427	98 7
C C 50 N M 1 1	C	(5 7)	(14 4)	33/14 (21)	113/75 (96)	109	2 79	75	4 51	1 56	46	1 94	612	2 580	91 4
	2	(5 1)	(11 3)	30/13 (19)	89 6 (69	136	3 52	10(	5 32	2 00	14	2 40	444	1 612	90 3
J G 58 N M 1 (0	C	(7 5)	(25 1)	(0/32 (41)	151/91 (99)	94	3 30	117	5 97	1 97	37	4 95	1 010	2 486	90 6
	2	(4 7)	(20)	55/27 (38)	170/60 (79)	100	4 09	137	5 81	2 37	40	5 21	901	1 665	88 4
W J 5 N M 1 82	C	(4 8)	(21 0)	55/23 (37)	11 /69 (93)	97	3 (9	128	4 24	3 03	4	7 01	531	1 206	(5 4
	2	(4 9)	(21 1)	53/24 (36)	100/63 (73)	106	1 53	140	4 46	3 15	43	7 42	503	1 017	76 1

[illegible]

The effects of "dry" heat on the circulation of man

General hemodynamics in patients with chronic pulmonary emphysema

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Data presented by us in a previous report [1] delineated the general hemodynamic effects of the exposure of resting patients with enlarged left ventricles, compensated and in failure, to a "dry" ambient environment of 98° ± 1 and 40 per cent humidity ±3 for a period of 2 hours. This exposure resulted in a significant fall in the pressures of the pulmonary and peripheral arterial beds with a decrease in the respectively calculated resistances; no change occurred in the oxygen consumption and the cardiac output. The calculated work of the left ventricle decreased. It was speculated that the short-term exposure to a warm *dry* environment was not deleterious to these patients, although Burch has repeatedly emphasized the ill effects of a *hot and humid* environment upon such individuals.

It is a common clinical observation that people suffering from chronic pulmonary disease are also poorly tolerant of hot and humid weather. Contrariwise, it appears important to know whether these people tolerate a warm and dry environment, at least in the resting state and for a brief period of time, as well as people with a diseased left ventricle[1] would appear to do. The current report presents the data gathered in 10 patients with chronic pulmonary emphysema who were subjected for 2 hours to an ambient temperature of 98° F. and a humidity of 40 per cent.

Materials and methods

Ten male patients who ranged in age from 39 to 63 years were studied. All had chronic pulmonary emphysema of varying severity, as gauged in all instances by a decreased total vital capacity, a reduction of the first second expiration time to less than 60 per cent, and increases in the total lung volume and residual functional volume to levels above 40 per cent of the predicted normal values. None of the patients had a demonstrably diseased left ventricle, and all were normotensive.

The details of procedure were identical to those previously reported for the patients with diseased left ventricles.[1] All studies were performed in the postabsorptive state, but in most instances small doses of chloral hydrate rather than a barbiturate were employed for sedation. After right-sided cardiac catheterization

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A V D	*Cardiac index*	pCO_2	*RVWk*	*P TR*	*ETPR*	*Peripheral arterial saturation (%)*
5 13	2 05	43 5	4 03	629	2 215	88 1
5 35	2 37	41 4	4 46	521	1 635	88 2
+4 3	+15 6	−4 8	+10 7	−17 2	−26 6	+0 1
< 05 > 02	< 001	< > 1	< 0 > 01	< 02 > 01	< 001	< 9
< 005 > 001	< 005 > 001	< 1 > 05	—	< 05 > 0	< 3 > 2	< 9

who were reported upon previously (Am Heart J 56 212 1958)

increases were noted in the minute ventilation the oxygen consumption the arteriovenous oxygen difference and the cardiac index The calculated work of the right ventricle was greater than 1 1 Kg M / min /M during the control period in all patients and increased significantly after the patients were exposed to the warm environment The calculated left ventricular work decreased (data omitted) The average rectal temperature increased by 1 6 F (data omitted) This was the same as that for the previously reported group of patients with enlarged left ventricles The calculated resistances decreased There was some decrease in arterial pCO although this was not significant The peripheral arterial oxygen saturation was initially below normal in all patients and showed no significant change

Discussion

The most important differences noted in these patients with pulmonary emphysema when compared to the ones previously reported are as follows (1) The pulmonary arterial pressure did not change in contrast to the significant decrease in the subjects with enlarged left ventricles (2) The cardiac index increased As a result the total pulmonary resistance decreased but did so significantly less than in the previous patients (3) Most important of all there was a significant increase in the calculated work of the right ventricle whereas that of the left ventricle decreased This is in marked contrast to the significant decrease in the calculated work of *both ventricles* in the previously reported patients and implies at least a relative lack of reactivity of the pulmonary vascular bed to the stimulus of heat in the emphysematous subjects

It was noted that the minute ventilation and the oxygen consumption increased in the emphysematous patients although this was not sufficient in magnitude to differ significantly from the response of the patients with enlarged left ventricles in whom no change was recorded The increase in minute ventilation was due only to the increase in the depth of respiration The reason for this increase in the ventilation is obscure Burch has demonstrated that in resting normal subjects as well as in those with left ventricular congestive heart failure the amount of pulmonary ventilation is increased but the rates of loss of water and heat from the skin are decreased when these individuals are exposed to a *hot and humid* environment.[8] This places an undue stress particularly on the cardiovascular system of the patient with congestive failure [1 7] Although a "dry

heat does not appear to affect similarly such individuals, it is obvious that patients with emphysema are harmed even by this situation. One wonders then whether in these emphysematous individuals with impaired alveolar ventilation and "puddling" of warm air in the lungs, a stimulus may not be provided which would favor loss of heat through the respiratory tract by increasing respiration and the excretion of carbon dioxide. The increased metabolic rate might represent in good measure a response to the increased work of respiration; these patients were not made irritable by the hot and dry atmosphere and, indeed, most of them dozed or slept quietly after the room temperature was elevated.

The data strongly suggest that hot weather, even though arid, is deleterious to patients with pulmonary emphysema and that the more severely ill ones should be placed in an air-conditioned environment. This in no way suggests preferential treatment for these patients when hospitalized and when air-conditioning facilities are limited, over those with congestive heart failure due to a diseased left ventricle, since the therapeutic value of cool, dry air for the latter group of patients has been well established.[6]

Summary

After right-sided cardiac catheterization, 10 resting male patients with chronic obstructive pulmonary emphysema were exposed to an ambient temperature of 98 F. and a comfortable humidity of 40 per cent for 2 hours. Restlessness and increased motor activity did not occur.

Whereas the brachial arterial pressure decreased significantly, the pulmonary arterial pressure did not change. The minute ventilation, oxygen consumption, cardiac output, and calculated work of the right ventricle all increased significantly.

The data suggest that patients with pulmonary emphysema tolerate poorly a hot environment, even though the humidity is low, and emphasize the need for air-conditioned surroundings in the management of these subjects during excessively warm weather.

REFERENCES

1. Berenson, G. S., and Burch, G. E.: The response of patients with congestive heart failure to rapid elevation of atmospheric temperature and humidity, Am. J. M. Sc. 223:45, 1952.
2. Burch, G. E.: Rate of water and heat loss from the respiratory tract of normal subjects in a subtropical climate, Arch. Int. Med. 6:315, 1945.
3. Burch, G. E.: The influence of environmental temperature and relative humidity on the rate of water loss through the skin in congestive heart failure in a subtropical climate, Am. J. M. Sc. 211:181, 1946.
4. Burch, G. E.: Influence of variation in atmospheric temperature and humidity on the rates of water and heat loss from the respiratory tract of patients with congestive heart failure living in a subtropical climate, Am. Heart J. 32:190, 1946.
5. Burch, G. E.: Influence of hot and humid environment on the patient with coronary artery disease, J. Chron. Dis. 4:350, 1956.
6. Burch, G. E., and DePasquale, N.: Influence of air conditioning on hospitalized patients, J.A.M.A. 170:160, 1959.
7. Burch, G. E., and Hyman, A.: Influence of a hot and humid environment upon cardiac output and work in normal man and in patients with chronic congestive heart failure at rest, Am. Heart J. 53:665, 1957.
8. Dexter, L., Whittenberger, J. L., Haynes, F. W., Goodale, W. T., Gorlin, R., and Sawyer, C. G.: Effect of exercise on circulatory dynamics of normal individuals, J. Appl. Physiol. 3:439, 1951.
9. Gorlin, R., Haynes, F. W., Goodale, W. T., Sawyer, C. G., Dow, J. W., and Dexter, L.: Studies of the circulatory dynamics in mitral stenosis. II. Altered dynamics at rest, Am. Heart J. 41:30, 1951.
10. Sancetta, S. M., Kramer, J., and Husni, E.: The effects of "dry" heat on the circulation of man. I. General hemodynamics, Am. Heart J. 56:212, 1958.
11. Traks, E., and Sancetta, S. M.: The effects of dry heat on the circulation of man. II. Splanchnic hemodynamics, Am. Heart J. 57:438, 1959.

Biventricular origin of the pulmonary trunk with subaortic stenosis above the ventricular septal defect

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Edwards and Becu and associates have described a developmental complex with biventricular origin of the pulmonary trunk and subaortic stenosis. The ventricular septal defect is located anteriorly in the outflow tract of the right ventricle without involvement of the membranous portion of the ventricular septum. The pulmonary artery is not transposed but overrides the ventricular septal defect. This malformation is also characterized by subaortic stenosis formed by a muscular ridge which lies across the outflow tract of the left ventricle and above the ventricular septal defect. Associated obstructive anomalies of the aortic arch are constant. In all cases previously described the patients died in early infancy from pulmonary hemorrhage and edema, although one of us (J. E. E.) has observed a similar malformation in a 35-year-old man.

The purpose of this paper is to describe the pathologic anatomic findings in three additional cases of this syndrome and to discuss the hemodynamics and clinical findings. Of further interest is the fact that in two of the three cases to be reported the patients were siblings (Cases 2 and 3) and identical pathologic malformations were found.

Report of cases

Case 1. An 8-year-old girl born of a normal pregnancy and an uneventful delivery appeared to be normal at birth. At 6 weeks of age diagnosis of congenital heart disease was made when the baby was found to manifest cardiac failure and be ... hospitalized. During the first 18 months of life the child was seriously ill and gained weight poorly. By the age of 2 years her general condition seemed to improve. At 3 years of age a large benign ovarian tumor was removed. In the following years remarkable improvement in her general condition was noted, but respiratory infections occurred frequently during the last few years of her life.

The patient was seen first at the Mayo Clinic in March 19[illegible]9 when she was 8 years of age. Examination at that time revealed a somewhat undernourished girl who appeared to be chronically ill. Other pertinent factors were as follows: absence of cyanosis and clubbing, normal femoral and radial pulses, no signs of congestive heart failure, overactivity of the heart with enlargement to the left, palpable second sound at the second left intercostal

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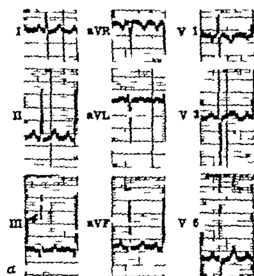




Fig 1 Case 1 The effects of left and right ventricular overload are shown by the electrocardiogram b Postero-anterior view of thorax showing cardiac enlargement and prominence of the main pulmonary artery segment

space no thrill normal first sound at the apex and narrowly split greatly accentuated second sound at the second left intercostal space A holosystolic murmur Grade 3 was heard at the lower left sternal border A different higher pitched systolic murmur Grade 2 was heard at the apex and was transmitted to the axilla and base of the left lung In addition, an apical mid-diastolic rumble was noted and there was a short high pitched low intensity insufficiency type of blowing diastolic murmur at the pulmonary area

An electrocardiogram (Fig 1) showed normal sinus rhythm with a rate of 95 and the mean manifest electrical axis of the QRS was +85 degrees The P R interval was 0 12 second The chest leads showed a RS pattern with negative T wave in Lead V and qRs pattern with positive T in Lead V. The electrocardiogram was interpreted as showing left ventricular overload and probable right ventricular overload

The roentgenographic examination showed moderate cardiac enlargement and increased pulmonary vasculature The pulmonary artery segment was prominent (Fig 1 b)

In December 1959 the right side of the heart was catheterized A synopsis of the data is presented in Table I

Of particular interest was an interatrial communication demonstrated by the passage of the catheter from the right atrium to the left atrium The catheter then passed from the latter chamber into the left ventricle The difference in oxygen saturation between samples of blood obtained from the pulmonary vein and from the left atrium suggested that a small right to-left shunt occurred at the atrial level A difference in pressure contour between the left atrium and the right atrium suggested that the communication was small either a valve-component patent foramen ovale or an exceedingly small atrial septal defect.

Also of interest were the measurements of pressures within the ventricles and the pulmonary artery compared to the pressure in the systemic artery Ten recordings of simultaneous pressures in the systemic arteries ventricles and pulmonary artery were taken All recordings showed that pressures in the ventricles and pulmonary artery were significantly in excess of pressures in the femoral and radial arteries

At the ventricular level both blood oxygen saturation and indicator-dilution curves indicated the presence of an interventricular communication with dominant right to-left shunt of approximately 45 per cent The systemic blood flow was 5 6 liters per minute per square meter of body surface in contrast to a pulmonary blood flow of 3 1 liters However when the patient breathed 100 per cent oxygen the pulmonary blood flow exceeded systemic blood flow

Table I Synopsis of data obtained during cardiac catheterization

Site	Pressure (mm Hg)	Oxygen saturation (per cent of capacity)
Superior vena cava	3	67
Inferior vena cava	—	71
Right atrium	3/-2	69
Right ventricle	—	65
Pulmonary artery	118/71	66
Left ventricle	103/0-5	85
Radial artery	83/63	84
Femoral artery	88/70	83
Right pulmonary vein	3/0	95

M an pressure

Fig. Case 1. Right ventricle (*R V*) and pulmonary trunk (*P T*) showing the relationship of the ventricular septal defect (*D*) to the pulmonary valve. The defect is immediately beneath the pulmonary valve. The biventricular origin of the pulmonary trunk is not so well appreciated in this perspective as in *c*. *b*, Left ventricular aspect. In the outflow tract of the left ventricle a ridge of muscle (*D R*) divides the outflow tract of the left ventricle into two portions. The anterior portion is that which communicates through the ventricular septal defect (*D*) with the pulmonary trunk. The posterior subdivision of the outflow tract of the left ventricle is bounded anteriorly by the aforementioned dividing ridge and posteriorly by the anterior leaflet of the mitral valve (*M*). The presence of the dividing ridge creates a stenotic subaortic tract. *c*, Sagittal section through the anterior walls of the two ventricles and through the ventricular septal defect to show the relationship of the two ventricles, the ventricular septal defect, and the pulmonary trunk. It is apparent that the pulmonary trunk has a position of biventricular origin and has communication with both ventricles. The left ventricular output is diverted partly through the ventricular septal defect to the pulmonary trunk and partly through the stenotic subaortic tract to the aorta. *d*, The aortic arch. The anterior wall has been removed; the viewer sees the specimen from the front toward the back. The branches are normal. Beyond the origin of the left subclavian artery and opposite the site of the ligamentum arteriosum the superior and posterior walls *show a small curtainlike infolding (arrow) which narrows* the lumen slightly and represents ... of the classic change in coarctation of the a...

by approximately 1.2 liters per minute per square meter of body surface. Under this circumstance a left-to-right shunt of moderate magnitude was demonstrated, but a right-to-left shunt still accounted for approximately 20 per cent of the systemic blood flow.

Because of the electrocardiographic evidence of left ventricular overload, the roentgenographic evidence of increased pulmonary vasculature, and the dominant left-to-right shunt when the patient breathed 100 per cent oxygen, it was decided to attempt surgical closure of the ventricular septal defect with the full appreciation of the high risk involved.

Surgical closure of the ventricular defect was carried out on March 3, 1960. No fall occurred in right ventricular pressure, and the patient died shortly after the operation was completed.

The essential findings at necropsy were limited to the cardiovascular system (Fig. 2). The heart showed the features of the developmental complex previously described. The pulmonary trunk lying above and anteriorly to the ventricular septal defect communicated with both ventricles (Fig. 2). Subaortic stenosis above the level of the ventricular septal defect was caused by a muscular ridge crossing the outflow tract of the left ventricle (Fig. *b* and). The aorta was continuous and the branches arose in normal fashion. A classic deformity of aortic coarctation was found just distal to the origin of the left subclavian artery (Fig. 2). The degree of obstruction was minimal and evidently was not sufficient to cause a significant difference in pressure between radial and femoral arteries. Histologic examination of the lungs showed hypertensive [pulmonary vascular] changes, Grade 4 [as] described by Heath and Edwards. A representative section is shown in Fig. 3. Characteristic findings were formations of plexiform lesions with dilatation of vessels, thickening of the media and intimal fibrosis.

Case 2. A newborn male infant died at the age of 3 days in 1958. The mother's pregnancy and delivery had been uncomplicated. On the second day after the infant's birth increasingly progressive cyanosis was noted (specific location not described).

Neither the femoral nor the radial pulse was palpable. The heart was quiet, with a rate of 120. The first sound was normal; the second sound was single and accentuated. No murmurs were audible.

The roentgenogram showed moderate enlargement of the heart with increased pulmonary vasculature (Fig. 4). In spite of supportive treatment the child died suddenly on the third day of life.

The electrocardiogram showed a normal sinus rhythm with a mean electrical axis of the QRS complex of +140 degrees. The tracing showed a normal degree of right ventricular hypertrophy for the patient's age (Fig. 4 *b*).

Case 3. The sister of the infant in Case 2 was born 2 years later in 1960. Again the mother's pregnancy and delivery had been uneventful. After delivery, hoarseness and differential cyanosis were noted in the child. Cyanosis was present and equal in the arms and feet but was not present in the cheeks. The child was placed in an oxygen tent, but the cyanosis persisted.

Blood pressures taken by the flush method were equal in the arms and legs. The cardiac rate was 140 beats per minute and the heart was overactive. The first cardiac sound was normal, and the second sound was narrowly split and accentuated.

A Grade 3 systolic murmur and a Grade 2 diastolic murmur were heard over the left side of the sternum.

Roentgenographic examination showed evidence of an enlarged heart and prominent pulmonary vasculature (Fig. 5). The electrocardiogram showed normal sinus rhythm. The mean value for the main frontal electrical axis was approximately +170 degrees (Fig. 5 *b*).

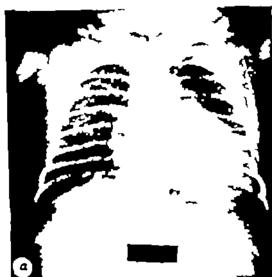
In spite of supportive treatment the child did not improve; she died on the third day of life.

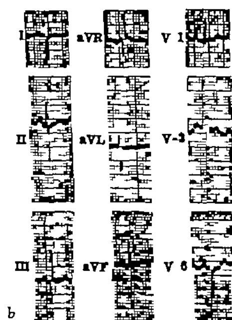
Pathologic examination of the heart and great vessels in this patient and the brother (Case 2) showed identical findings (Fig. 6). Therefore they are described together.



Fig. 3. Case 1. A large muscular artery showing medial hypertrophy. *a*, With pronounced nonspecific intimal fibrous thickening (hematoxylin and eosin, ×75). *b*, With plexiform lesion (in lower left hand corner) (hematoxylin and eosin, ×100).







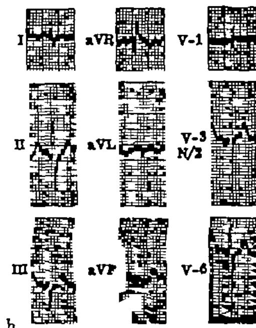


Fig 4 Case I osteroanterior iew of thorax showing cardiomegaly with increased pulmonary asculature b Normal sinus rh thm ith mean lectric l xis of the QRS complex of +140 degrees

Fig 5 Case 3 Posteroanterior iew of thorax showing cardiomegaly with increased pulmonary asculature b Normal sinus rhythm ith mean electrical axis of +120 degrees

PATHOLOGIC FINDINGS IN CASES 2 D 3 I each case the heart showed entricular septal defect in the basal portion of the entricular septum t anterior position abov the cri ta supraventricularis The defect was close to the origin of the pulmonary trunk and the latter exhibited biventricular origin ... of its close ociation with the entricular septal defect (Fig 7,a and b)

A muscular crest divided the outflow tract of the left entricle into tw portions one leading to the entricular septal defect and the ther representing stenotic subaortic tract abov which arose the aorta (Fig 6) The ascending aorta ended by divid ing into the tw common carotid arteries

The pulmonary trunk was wide and g the tw pulmonary arteries after hic

arteriosus led into the descending aorta (Fig. 8,a and b). The left and right subclavian arteries arose from their respective sides of the descending aorta below the level of the ductus arteriosus. The right subclavian artery passed behind the esophagus to reach a normal position in the right axilla. There was no ductus arteriosus on the right side (Figs. 8,c and 9). Histologic examination of the lungs in Cases 2 and 3 showed vascular changes Grade 1 as described by Heath and Edwards. The media of the muscular pulmonary arteries was thickened, intimal fibrosis was not present but the adventitia was thick and fibrous. The type of change was that associated with pure left-to-right shunts among patients who have ventricular septal defect (Fig. 10).

Comment

Pathologic-anatomic features. In this complex the ventricular septal defect lies anterior to the membranous portion of the ventricular septum and above the papillary

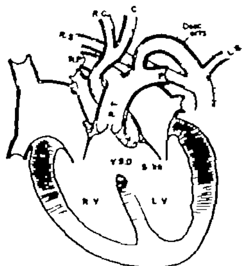


Fig. 6. Diagrammatic portrayal of the essential anatomic features within the heart in Cases 1, 2 and 3 and of the arrangement of the great vessels in Cases 2 and 3. There is biventricular origin of the pulmonary trunk above the ventricular septal defect. A dividing ridge creates a stenotic subaortic tract above which arises the ascending aorta. In these particular instances (Cases 2 and 3) there was interruption of the aortic arch wherein the ascending aorta terminated by dividing into the right and left common carotid arteries (*R.C.* and *L.C.*). The descending aorta communicates with the pulmonary arterial system by way of a patent ductus arteriosus. The two subclavian arteries arise opposite each other from the upper portion of the descending aorta. The right subclavian artery (*R.S.*) passed behind the esophagus to reach the right side of the body. In this particular instance supply of the descending portion of the body and of the subclavian arteries by the right ventricle was the basis for cyanosis of the arms and lower portion of the body whereas the head failed to show this abnormal sign.

muscle of the conus. From the right ventricular view the defect opens into the distal portion of the right ventricular outflow tract. A portion of the upper edge of the defect is formed by the pulmonary valvular tissue at the commissure between the left and right pulmonary cusps.

The outflow tract of the left ventricle is divided by a muscular ridge which runs from the base of the anterior leaflet of the mitral valve to the anterior wall of the left ventricle. This muscular ridge divides the outflow tract of the left ventricle into two parts, a narrow subaortic tract beyond which the aorta arises and a part which is connected with the ventricular septal defect.

Additional obstructive malformations of the aorta were noted in all cases in which the intracardiac malformations described in this paper and in previous reports are present. Some cases are associated with interruption of the aortic arch, others show coarctation or hypoplasia of the aortic arch. Anomalous origin of the right and left subclavian arteries from the descending aorta represents the early embryonic onset of this defect. Another interesting feature in the cases presented herein is the occurrence of the same malformation in siblings.

Hemodynamics. Becu and associates emphasized that in this anomaly a left to right shunt at the ventricular level probably exists during fetal life because of the subaortic stenosis above the ventricular septal defect. Such a shunt would reduce aortic flow and increase pulmonary flow. Under these circumstances the pulmonary trunk dilates and overrides progressively. The reduced flow through the aorta, on the other hand, might be responsible for the tendency toward hypoplasia or possibly even toward interruption of the aortic arch. Data do not establish these points, and the aortic malformation may be derived from the same stimuli which cause the intracardiac malformation.

Case 1 in this series is, to the best of our knowledge, the first case reported in the literature in which catheterization data were interpreted. The physiologic study showed the interesting features discussed below.

The finding of a consistently higher pressure in the right and left ventricles and pul

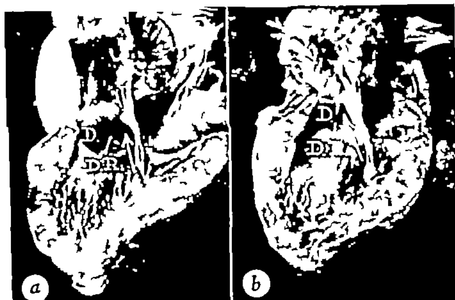


Fig 7 The left ventricular outflow tracts in the siblings (Cases 2 and 3) show the virtually identical structural abnormalities of the two cases *a* Case 2 *b* Case 3 The perspective is essentially that shown in Fig 2 *b* (Case 1) The dividing ridge (*D R*) separates the outflow tract of the left ventricle into two channels one leading to the ventricular septal defect (*D*) and the other posteriorly to the stenotic subaortic tract (*arrow*)

monary artery than in the systemic arteries is of great significance in establishing the diagnosis of the intracardiac malformation in this instance In a comparison of simultaneously recorded aortic and radial arterial pressures Kroeker and Wood have shown that amplification of the systolic peak at the peripheral artery occurs in an average of 11 per cent Thus for example a pressure pulse recorded simultaneously at the aortic root and radial artery could be expected to show pressure values of 100 and 110 mm Hg systolic respectively The converse is rarely if ever seen Occasionally in patients with rheumatic heart disease in whom the cardiac output is reduced or in patients with severe aortic stenosis and reduced cardiac output pressures in the systemic and central arterial circulations may be equal In Case 1 however we found a significant difference Although the ventricular pressures were equal and were transmitted without diminution into the pulmonary artery these pressures significantly exceeded the systemic arterial pressure If any systolic amplification occurred in this case the true pressure gradient between the ventricles and the aortic root would have been somewhat greater than the given values suggested initially

All other conditions being unaltered the combination of subaortic or aortic valvular stenosis above a ventricular septal defect should lead to a marked increase in pulmonary blood flow However as with other cases of ventricular septal defect there is no reason why progressive and severe pulmonary vascular disease should not develop in such patients so that the increased resistance offered to ejection of blood from the ventricles through the aortic valve might become balanced by increased pulmonary resistance and might even be exceeded by the resistance offered by the diseased pulmonary vascular bed As a result even though the pressure relationships would remain the same the magnitude of the left to right shunt would fall If the pulmonary vascular resistance became higher than the resistance to flow through the aortic valve a right to left shunt might appear Such phenomena appear to have developed in Case 1

The histologic changes in the pulmonary vessels found in Case 1 showed Grade 4 changes (Fig 3)[4] and were compatible wi

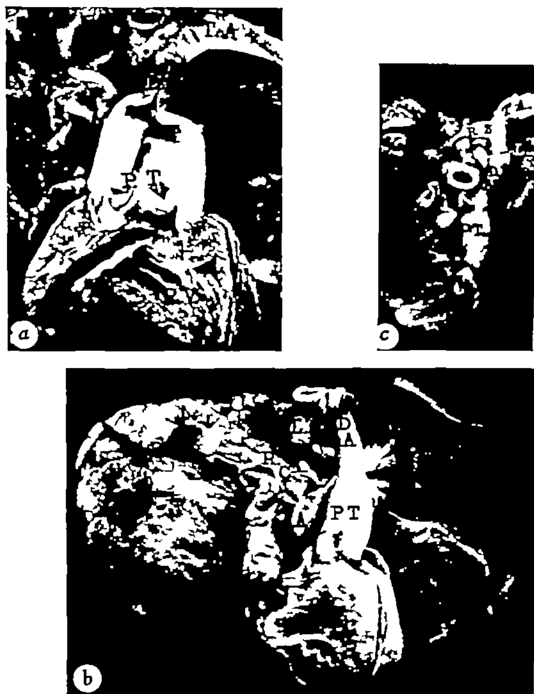


Fig. 8. Case . The features shown are essentially like those observed in Case 3. *a*, Right ventricle and great vessels. The ventricular septal defect which lies immediately beneath the origin of the pulmonary trunk (*P.T.*) is seen from the right ventricular aspect (*R.V.*). In this instance, as in all others of this developmental syndrome, the pulmonary trunk showed biventricular origin. The ascending aorta (*A.*) is divided into its two terminal branches, the two carotid arteries. The thoracic portion of the descending aorta (*T.A.*) has no connection with the ascending aorta and takes origin from the pulmonary arterial system by way of the ductus arteriosus (*D.A.*). *b*, Anterior view of heart and great vessels showing the termination of the ascending aorta (*A.*) into the right common carotid (*R.C.*) and the left common carotid (*L.C.*) arteries. The pulmonary trunk is wide and the ductus arteriosus (*D.A.*) represents the channel of continuity between the pulmonary arterial system on the one hand and the descending aorta on the other. *c*, The great vessels viewed from below, showing the continuity of the descending thoracic aorta (*T.A.*) with the pulmonary arterial system (*P.T.*) by way of the patent ductus arteriosus (*D.A.*). The left subclavian artery (*L.S.*) and the right subclavian artery (*R.S.*) both arise from the descending thoracic aorta beyond the ductus arteriosus. In this perspective the position of the right subclavian artery behind the trachea and esophagus is shown.

severe elevation of pulmonary vascular resistance

In the two cases with interruption of the aortic arch (Cases 2 and 3) the hemodynamics must have differed from those in Case 1 In Cases 2 and 3 it is assumed that only left to right shunts existed within the heart In these two patients both ventricles and the pulmonary artery were in the same systolic compartment The ascending aorta was separated from this compartment proximally by the subaortic obstruction and distally by the interruption of the aortic arch Since the ascending and the descending aorta are separated the blood supply to the descending aorta comes from the pulmonary artery via the ductus

We can assume that the systolic pressure was equal in both ventricles in the pulmonary artery and in the descending aorta whereas the pressure in the ascending aorta must have been lower than in these vascular segments or ventricles

If both subclavian arteries arise below the interruption of the arch as in Cases 2 and 3 the pressures in the brachial and femoral arterial systems would be equal and higher than those in the arteries supplying the neck and head The arms and legs receive blood from the pulmonary artery through the ductus and the head receives its supply from the ascending aorta

In patients with anatomic arrangements like those in Cases 2 and 3 cyanosis may be seen only in those parts of the body supplied by the aorta beyond the interruption Depending on the degree of left to right or right to left shunt at the ventricular level cyanosis seen in the portion of the body supplied by the proximal aorta may be of a different degree (less blue) than that (bluer) seen in the portion of the body supplied by the descending aorta

The recognition of this entity and its differentiation from the more commonly encountered ventricular defect with pulmonary hypertension is of some practical importance In the assessment of the operability of patients with ventricular septal defect and pulmonary hypertension the electrocardiographic finding of left ventricular overload has been of great assistance as an indication of the presence of a dominant left to right shunt It is imperative to exclude other causes of left ventricular overload particularly those associated with aortic stenosis or mitral insufficiency In Case 1 these lesions were considered but the typical murmur of aortic stenosis could not be distinguished from the prominent murmur of ventricular septal defect In retrospect the consistent elevation of ventricular and pulmonary arterial pressures above systemic pressure should have led to a more careful consideration of the presence of aortic or subaortic stenosis

Summary

Three cases are reported that presented a complex of congenital cardiac anomalies which consisted of biventricular origin of the pulmonary trunk with subaortic stenosis above a ventricular septal defect In Case 1 the hemodynamic findings obtained at cardiac catheterization showed consistently higher ventricular and pulmonary arterial pressures when these were compared to systemic arterial pressure Two patients were siblings with identical anatomic findings (Cases 2 and 3) Both of these patients had associated interruption of the aortic arch The descending aorta which

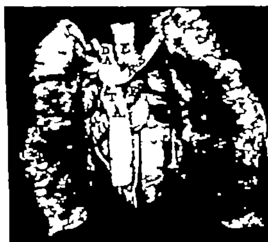


Fig 9 Posterior [illegible] view of the heart and lungs (Case 3) showing arrangements which were duplicated in Case 2 The descending thoracic aorta (*T A*) takes origin from the ductus arteriosus (*D A*) which represents the channel of communication between the descending thoracic aorta and the pulmonary arterial system The two subclavian arteries are seen to arise from the upper portion of the descending aorta just beyond its origin in the ductus arteriosus *L S* Left subclavian artery The right subclavian artery (*R S*) passes behind esophagus (*E*) to reach the right side of



Fig 10 Case 3 A muscular artery has been cut in both cross and longitudinal section The vessel shows medial hypertrophy and prominent endothelial cells but no intimal fibrosis (elastic tissue stain ×200)

gave rise to the subclavian arteries communicated with the right ventricle through a patent ductus arteriosus In one of the patients (Case 3) differential cyanosis was noted the upper and lower extremities were cyanotic but the head was not cyanotic Mild coarctation of the aorta was present in the third patient (Case 1)

REFERENCES

1 Edward J E Congenital malformations of the heart and great vessels I Gould S E Pathology of the heart Ed. 1 Springfield Ill 1953 Charles C Thomas p 560
2 Becu L M Tauxe W N DuShane, J W and Edward J E A complex of congenital cardiac anomalies ventricular septal defect, biventricular origin of the pulmonary trunk, and subaortic stenosis Am Heart J 50 901 1955
3 Lauer R M DuShane J W and Edwards J E Obstruction of left ventricular outlet in association with ventricular septal defect Circulation 22 110 1960
4 Heath D and Edwards J E The pathology of hypertensive pulmonary vascular disease A description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects Circulation 18 533 1958
5 Kroeker E J and Wood E H Comparison of simultaneously recorded central and peripheral arterial pressure pulses during rest exercise and tilted position in man Circulation Res. 3 623 1955

The auscultatory findings in primary myocardial disease

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Auscultation of the heart has been of great value in the clinical diagnosis and evaluation of patients with primary myocardial disease. The myocardial abnormalities in this category occur in the absence of acquired valvular heart disease, coronary artery disease, hypertension, or congenital malformations.[illegible] The group includes (1) myocarditis[10] (associated with infectious diseases, collagen diseases, sarcoidosis, physical agents, toxic agents, and of unknown cause), (2) myocardial hypertrophy of unknown etiology,[11] (3) infiltrative diseases of the myocardium[illegible] (neoplasms, amyloidosis, etc.), (4) nutritional cardiopathy,[illegible] (5) endocardial fibroelastosis,[illegible] (6) endomyocardial fibrosis,[illegible] (7) familial cardiomegaly,[illegible] (8) metabolic heart disease (thyrotoxicosis, hemochromatosis, glycogen storage disease, gargoylism, etc.), (9) cardiomyopathies associated with neuromuscular disorders[illegible] (progressive muscular dystrophy, dystrophia myotonica, Friedreich's ataxia). The auscultatory features are outlined in Table I; they are the results of conduction defects, ectopic rhythms, myocardial failure, or associated pericardial involvement. A combination of these findings is frequently present.

Diastolic gallop rhythm, ventricular and/or atrial, is common (Figs. 1-5, 7). At times the two gallop sounds may coincide, resulting in a summation gallop rhythm. In the presence of congestive heart failure, a ventricular gallop has been a constant finding. An atrial gallop is frequently observed and may be more evident with delayed atrioventricular conduction. However, the atrial gallop may occur even when the P-R interval is normal. The diagnosis of primary myocardial disease should be considered when a patient with heart disease presents with a ventricular and/or atrial diastolic gallop, cardiomegaly, and other symptoms or signs of cardiac decompensation unexplained by the usual causes of heart disease. The pulmonary second sound is generally increased in the presence of cardiac decompensation (Fig. 1, right lower strip). Occasionally, the combination of both ventricular and atrial diastolic gallop sounds produces a diastolic rumble which simulates mitral stenosis. In fact, the patient whose tracings are shown in Fig. 2 was thought to have rheumatic mitral stenosis and was referred to our hospital to be evaluated for commissurotomy. After a complete study, including cardiac catheterization, the diagnosis of idiopathic myocarditis was made. She has been followed in the Cardiac Clinic for

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the past 6 years and has shown definite improvement on steroid therapy which resulted in a diminution of heart size disappearance of the gallop rhythm and marked symptomatic improvement When the steroids were discontinued her symptoms and signs of heart failure including gallop rhythm and the diastolic rumble reappeared In addition complete heart block developed These features again regressed with reinstitution of corticoid therapy

The ventricular diastolic gallop has been a constant finding in patients with cardiac decompensation and often has been one of the first clues indicating the presence of heart failure The patient may subsequently improve with the institution of digitalis restriction of sodium and diuretics At other times only an atrial gallop is noted as illustrated in Fig 3 (left lower tracing) in a 25 year old man with cardiac enlargement and right bundle branch block Cardiac catheterization disclosed no unusual

Table I Auscultatory abnormalities in myocarditis

Conduction Defect

- I A V node
  - A P R interval prolongation
    - 1 Decreased intensity of S_1
    - 2 Atrial gallop rhythm
    - 3 Atrial sound with prolonged vibration (atrial murmur)
  - B Second degree heart block
    - 1 Isolated atrial sound
  - C Complete heart block
    - 1 Variation in intensity of S_1
    - 2 Atrial sounds
- II Bundle branch block
  - A Right bundle branch block
    - 1 Delay in P_2 with wide splitting of S_2
  - B Left bundle branch block
    - 1 Delay in A_2 with paradoxical splitting of S_2

Ectopic Rhythms

- I Extrasystoles
  - A Atrial premature contractions
  - B Ventricular premature contractions
- II Atrial fibrillation
- III Ventricular tachycardia
  - A Multiple sounds and variation in intensity of S_1
    - 1 Combination of atrial gallop split S_1 split S_2 and ventricular diastolic gallop

Myocardial Failure

- I Gallop rhythm
  - A Ventricular diastolic gallop
  - B Summation gallop—fusion of atrial and ventricular diastolic gallops
  - C Mid diastolic murmur
    - 1 Ventricular diastolic gallop with prolonged vibrations
    - 2 Proximity of atrial and ventricular diastolic gallops
- II Pulmonary hypertension
  - A Narrow splitting of S_2 with loud P_2
- III Relative atrioventricular valvular insufficiency
  - A Mitral insufficiency
  - B Tricuspid insufficiency

Associated Pericarditis

- I Pericardial friction rub
  - A Two components
    - 1 Sinus rhythm—ventricular systolic and atrial components
    - 2 Atrial fibrillation—ventricular diastolic and ventricular systolic components
  - B Three components
    - 1 Sinus rhythm—atrial ventricular systolic and ventricular diastolic components

findings No signs of heart failure were present during this period of observation but several years later his physician reported that he had been admitted to another hospital because of pulmonary edema Various examples of primary myocardial disease are shown in Figs 1 through 8 Fig 4 shows the tracings of two patients with lupus erythematosus one case with sarcoidosis and the other of unknown cause The patient with myocardial disease of unknown cause (autopsy) whose tracings are shown in Fig 1 was followed for several years and both atrial and ventricular diastolic gallops were observed clinically At times a diastolic rumble was heard and at other times particularly when the rate was rapid a type of summation gallop rhythm appeared A faint systolic murmur at the cardiac apex was generally present and a greatly accentuated pulmonic second sound with close splitting of the second heart sound was heard in the pulmonary area and at the left sternal border

A systolic murmur is a frequent finding in primary myocardial disease (Figs 1 through 6) and represents either an innocent outflow ejection murmur or a pansystolic murmur of relative mitral and or tricuspid valvular insufficiency The murmur generally varies between Grade 2 and Grade 4 (on the basis of grading 1 through 6) and often leads to the erroneous diagnosis of rheumatic heart disease such as mitral insufficiency or a congenital malformation such as ventricular septal defect A patient recently observed had a Grade 3 to 4 pansystolic murmur best heard at the lower left sternal border and transmitted to the left axilla lung bases and lower left

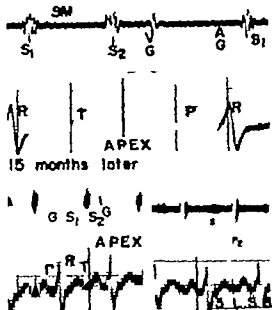


Fig 1 Thirt en year-old ma who had progressive refractory heart failure for approximately 1½ years before death Upper tracing Note atrial (AG) and ventricular (VG) diastolic gallops and systolic murmur (SM) Fifteen months later (lower strips) he had advanced heart failure summation gallop (G) and loud nd sound (P) Autopsy finding hronic m ocarditis nd ape hi

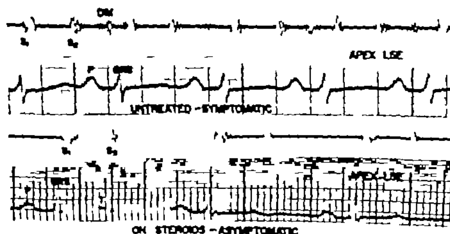


Fig 2 Thirty n ear-old woman with chronic idiopathic myocarditis controlled on steroid therapy Upper tracing Congestive failure Note diastolic rumble (DM) Lower tracing No failure On steroid No murmur or gallops

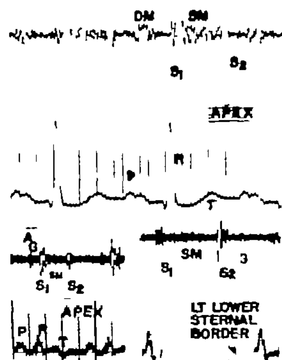


Fig 3 Fibroelastosis—3 cases (2 suspected and 1 definite) *Upper tracing* 2½ year-old girl with fibroelastosis (proved by biopsy) and coarctation Note systolic murmur (*SM*) and diastolic rumble (*DM*) *Lower left tracing* 25 year-old man with cardiac enlargement atrial gallop (*AG*) and right bundle branch block who had Grade 2 to 3 apical systolic murmur (*SM*) Normal cardiac catheterization He had pulmonary edema several years later *Lower right tracing* Infant girl 3 months of age with congestive failure râles and hepatomegaly Note systolic murmur (*SM*) and gallop (*G*)

interscapular region There was no evidence of a shunt or of organic valvular disease at the time of catheterization of the right and left sides of the heart A ventricular diastolic gallop was present at the apex Primary myocardial disease probably fibroelastosis was suspected Fig 7 illustrates tracings from two patients with myocardial disease of unusual origin one patient had Wegener's granulomatosis[30] and the other had obscure eosinophilia and some clinical features suggestive of restrictive myocardial disease such as seen in constrictive pericarditis[31]

The presence of conduction defects such as right or left bundle branch block may produce abnormal splitting of the first and second heart sounds In complete right bundle branch block wide splitting of the second heart sound during expiration with further increase in splitting during inspiration (Fig 8) is characteristic[32] and is best heard at the pulmonary area and at the third intercostal space left sternal border In addition the first heart sound is frequently widely split With complete left bundle branch block[4] the splitting of the second sound is paradoxical (reversed sequence of semilunar valvular closure) re

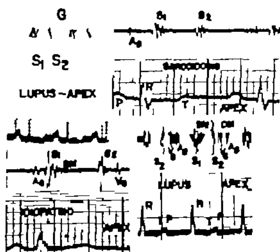


Fig 4 Myocardial disease in 4 patients Note frequency of gallop rhythm (*G A* and *Vg*) Systolic murmur (*SM*) in lower two Diastolic rumble (*DM*) heard in one (*lower right*)

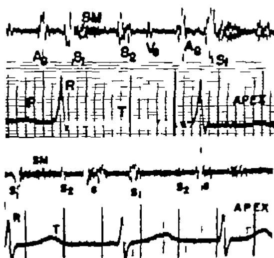


Fig 5 Thyrotoxicosis in 2 patients *Upper tracing* 38-year-old woman Note atrial (*AG*) and ventricular (*VG*) gallops and systolic murmur (*SM*) *Lower tracing* 42 year-old man Atrial fibrillation Note systolic murmur (*SM*) ventricular gallop (*G*) had several components producing a rumble quality

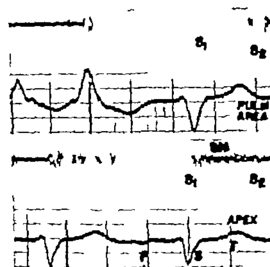


Fig. 6 Chronic myocarditis idiopathic in a 55 year-old man who had conduction defect short paroxysms of ventricular irregularity Note pan systolic murmur (SM) at apex (lower tracing)

sulting in a widely split second sound during expiration and a single or closely split second sound during inspiration Thus abnormal splitting of sounds may be heard in conjunction with gallop rhythm and other auscultatory findings already discussed

The majority of our patients have had a regular sinus rhythm but occasionally an arrhythmia is the earliest manifestation of primary myocardial disease Fig 9 shows the electrocardiogram of a 17 year-old boy who had a grossly irregular ventricular rhythm due to the presence of multifocal ventricular premature contractions and at times atrioventricular dissociation This patient s arrhythmia started when he had Asian influenza 2 years prior to admission Three days after this electrocardiogram was taken the patient died suddenly Postmortem examination revealed chronic interstitial myocarditis with patchy areas of subendocardial fibrosis In other patients various arrhythmias including atrial fibrillation or ventricular tachycardia may contribute to the abnormal auscultatory findings Fig 10 represents a composite of the auscultatory manifestations of primary myocardial disease These features may be observed individually or in various combinations and together with the complete clinical evaluation of the patient they often enable the physician to suspect the

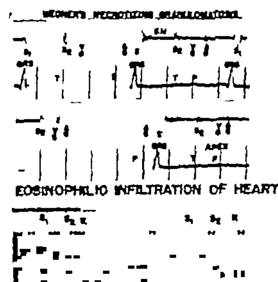


Fig 7 Two patients with myocarditis of unusual origin Upper two strips are continuous tracing of 44 year-old woman Note faint systolic murmur (SM) Atrial (AG) and ventricular (VG) gallops vary with change in P R relationship When gallops are close rumble quality is produced Lower strip 26 year-old man with heart failure of obscure origin Had marked eosinophilia and findings consistent with restrictive myocardial lesion Had loud diastolic knock sound (K) Systolic murmur was also heard

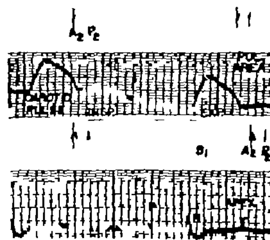


Fig 8 Fifty two-year-old man with hemochromatosis right bundle branch block. Wide splitting of second sound increased slightly on inspiration. He also had a faint apical first sound (S) and ventricular gallop.

*Our appreciation is expressed to Dr Jack P Segal Clinical Assistant Professor of Medicine, Georgetown University Medical Center for his permission to include this case.

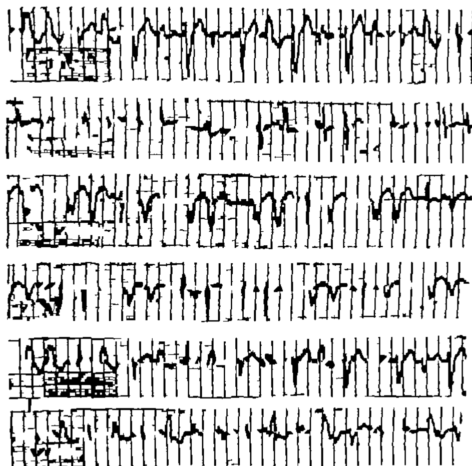


Fig. 8. A 17 year-old boy with the history of an arrhythmia which began after he had had Asian flu 2 years prior. Two days after this electrocardiogram was taken the patient died suddenly.

presence of primary myocardial disease early in its course.

Summary

The auscultatory abnormalities in primary myocardial disease have been reviewed. These abnormalities occur as manifestations of conduction defects, ectopic rhythms, myocardial failure, and associated pericarditis.

REFERENCES

1. Levine S and Harvey W P. Clinical auscultation of the heart, ed 2, Philadelphia, 1959, W B Saunders Company.
2. Mattingly T W. The clinical and hemodynamic features of primary myocardial disease, Tr Am Clin & Climatol A 70:132, 1958.
3. Brigden W. Uncommon myocardial diseases. The noncoronary cardiomyopathies, Lancet 2:1179 and 1243, 1957.
4. Burchell H B. Unusual causes of heart failure, Circulation 21:436, 1960.
5. Burchell H B. The diagnosis of unusual forms of heart disease, Cincinnati J Med 38:465, 1957.
6. Saphir O W M and Manion W C. Myocarditis—a frequent complication of many tenuous disease. Pamphlet, Publication Armed Forces Institute of Pathology, Washington, D C.
7. Saphir O. Myocarditis, Arch Path 33:88, 1942.
8. Pearce J M. Heart and filterable viruses, Circulation 21:448, 1960.
9. Hamme R K. Diffuse interstitial myocarditis in children, Am J Path 24:1235, 1948.
10. Burch G E and Walsh J J. Cardiac enlargement due to myocardial degeneration of unknown cause: preliminary report on effect of prolonged bedrest, J A M A 172:207, 1960.
11. Elster S, Horn H and Tuchman L R. Cardiac hypertrophy of unknown etiology, Am J Med 18:900, 1955.
12. Hurst J W and Cooper H R. Neoplastic diseases of the heart, Am Heart J 50:782, 1955.
13. Goudie R B. Secondary tumor of the heart and pericardium, Brit Heart J 27:183, 1955.
14. Erdoff J K. Cutaneous, cardiac and gastrointestinal manifestation of [illegible] syndrome, J Mt Sinai Hosp 21:193, 1954.

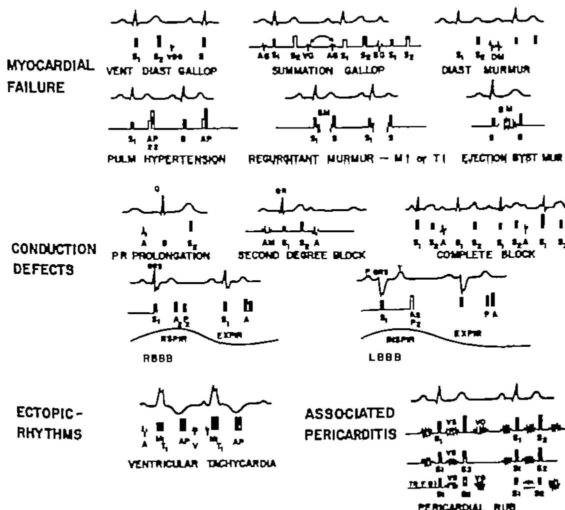


Fig *10* Componts of arious uscultatory bnormalities myocardial d ease

15 Benson R and Smith J Cardiac am lodoses Brit Heart J 18 579 1956

16 Blankenhorn M Vilter C Scheinker I and Austin R S Occidental ben ben heart disease J A M A 131 717 1946

1 Gillanders A D Nutritional heart disease Brit Heart J 13 177 1951

18 Higgenson J Gillanders A D and Murray J F The heart chronic malnutrition Brit Heart J 14 213 1952

19 Thomas W A Randall R V Bland E F and Castleman B Endocardial fibroelastosis factor in heart disease of obscure etiology New England J Med 2 1 3 7 1954

20 Gray I I Endocardial fibro Brit Heart J 13 387 19 1

21 Bedford F nd Konstam G Heart failure of unknow etiology in African Brit Hea t J 8 236 1946

22 E ans W F amilial cardiomegaly Brit Heart J 11 68 1949

3 Sandler G nd Wilson G The nature and progno is of heart disease in thyrotox co Quart J Med 28 347 1959

24 Lewis H Cardiac involvement in hemochromatosis Am J M Sc 22 544 1954

25 diSant Agnese P Andersen D and Mason H Glycogen storage disease of the heart critical review of the literature Pediatrics 6 607 1950

26 Emanuel R Gargoylism with cardiovascular m ol ement Brit Heart J 16 417 1954

27 Rubin I and Buchberg A The heart in progressive muscular d strophy Am He rt J 13 161 1952

28 E ans W The heart in myotonia trophica B t Heart J 6 41 1944

29 E ans W and Wright G Electrocardiogram in Friedreich disease Brit Heart J 4 91 1942

30 Go don G Gechman E Rosengarten R nd Neptune A Wegener granulomatos Ann Int Med 4 1260 1957

31 Clark G Valentine E and Blount S Endocardial fibrosis simulating constricti peri cardit report of a case ith determ nations of pre sure in the right side of the heart nd eosinophil New England J Med 2 1 349 1956

3 Leatham A Spl tting of the first nd second heart sound Lancet 2 607 1954

Experimental and laboratory reports

Effects of ischemia and hypoxia on the specialized conducting system of the canine heart

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Normal cardiac function depends upon the integrity of the specialized conducting system as well as on the performances of the contractile elements. In previous studies of the effects of ischemia on the heart, emphasis has been placed on changes in the electrocardiogram and in the ability of the heart to maintain an adequate circulation during and after periods of ischemia of varying duration.[1,2] However, these studies did not show whether observed impairment of function resulted from changes in the myocardium or in the specialized conducting system. Electrical activity of the isolated heart during ischemia has been studied with intracellular microelectrodes, and changes in the transmembrane potentials of single ventricular fibers have been observed.[3] Records from the specialized conducting system, however, were not obtained. Since ischemia involves more than a lack of oxygen, the effects of interruption of the circulation would be expected to differ from those of hypoxia alone. This difference has been observed in experiments concerned with the electrical activity of isolated preparations of cardiac tissue.[4] Nevertheless, the terms *ischemia* and *hypoxia* often are used interchangeably.

In the present studies the electrical activity of the intact in situ specialized conducting system has been recorded directly through multiple electrodes attached to the endocardium under direct vision during cardiopulmonary bypass. The effects of periods of ischemia which lasted 15 to 60 minutes have been compared to those which resulted from periods of moderate and severe hypoxia which lasted 60 or 120 minutes. The different results obtained from these two types of experiments suggest that ischemic changes in conduction result in large part from factors other than a lack of oxygen.

Method

Ten adult mongrel dogs which weighed between 20 and 30 kilograms were anesthetized with intravenous thiopental sodium, 25 mg. per kilogram of body weight. The animals were placed in the supine position, intubated with a cuffed endotracheal tube, and placed on a Jefferson respirator. The

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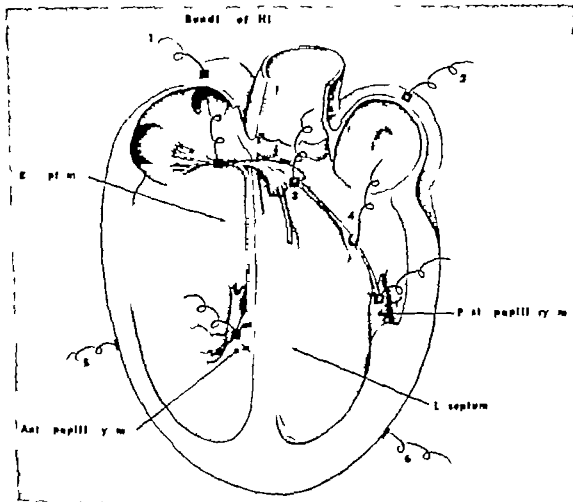


Fig 1 Semischematic diagram of the heart indicating the positions of the various electrodes used in the experiment 1 2 5 and 6 are the epicardial electrodes on the atria and ventricles 3 is on the left bundle branch and 4 is on the posterior free-running Purkinje fibers (false tendon) of the left bundle branch

rectal temperature was monitored with a Tele thermometer and arterial blood pressure was recorded from the left femoral artery with a Statham transducer and Sanborn recorder A standard limb lead electrocardiogram was monitored at all times and recorded in some experiments The chest was entered transsternally through the fifth intercostal space and the pericardium was opened widely The azygos vein and the superior and inferior venae cavae were isolated and tapes were placed about them The animals were then heparinized with 2 5 mg per kilogram of body weight Cardiopulmonary bypass was effected through an arterial cannula inserted into the right femoral artery and venous catheters inserted into the superior vena cava via the azygos vein and directly into the inferior vena cava A Dennis oxygenator[4] with an occlusive roller pump was used to maintain a mean arterial blood pressure of approximately 100 mm Hg at pump flows which ranged from 70 to 100 ml per kilogram per minute An attempt was made to keep the rectal temperature between 37 and 38 C by means of a Brown Harrison heat exchanger included in the arterial circuit

Electrodes consisting of acrylic plaques containing 3 to 16 silver wires 0 38 to 0 76 mm in diameter with the contacts separated by distances of 0 3 to 1 0 mm were sutured to the epicardial and endocardial surfaces of the heart with No 5 O atraumatic silk sutures (Fig 1) The

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In the present studies the electrical activity of the intact in situ specialized conducting system has been recorded directly through multiple electrodes attached to the endocardium under direct vision during cardiopulmonary bypass. The effects of periods of ischemia which lasted 15 to 60 minutes have been compared to those which resulted from periods of moderate and severe hypoxia which lasted 60 or 120 minutes. The different results obtained from these two types of experiments suggest that ischemic changes in conduction result, in large part, from factors other than a lack of oxygen.

Method

Ten adult mongrel dogs which weighed between 20 and 30 kilograms were anesthetized with intravenous thiopental sodium, 25 mg. per kilogram of body weight. The animals were placed in the supine position, intubated with a cuffed endotracheal tube, and placed on a Jefferson respirator. The

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fiers were employed to eliminate low frequency components of the tracer and to emphasize the electrographic deflections which result from activity of the specialized fibers [7] If a left ventriculotomy was not performed the left atrium was opened to avoid overdistention of the left ventricle during fibrillation Blood from the coronary sinus was drained back to the oxygenator by means of a tube placed in the right posterolateral aspect of the chest A thermistor was inserted into the right ventricular cavity to monitor the temperature within that chamber In several experiments a Walton Brodie strain gauge arch was sutured to the ventricular wall to record myocardial contractions

In seven experiments the effects of ischemia were studied by cross-clamping the ascending aorta for periods of 15 30 45 or 60 minutes Records were made at frequent intervals during the interruption of coronary perfusion and after removal of the aortic clamp To study the effects of hypoxia a mixture of 50 per cent oxygen and 50 per cent nitrogen was substituted for the mixture of 97 per cent oxygen and 3 per cent carbon dioxide ordinarily used in the oxygenator The substitution was made for a period of 120 minutes in one experiment in two others 100 per cent nitrogen was used for periods of 60 and 120 minutes respectively Again records were made at frequent interval during hypoxia and for 60 minutes after returning to a gas mixture of 97 per cent oxygen and 3 per cent carbon dioxide Arterial and venous oxygen saturations were determined by the Van Slyke–Neill method before and at selected intervals during the hypoxic periods

Results

Electrograms recorded through the electrodes located at the various sites on and within the heart were similar to those described previously [11] Records obtained from the epicardial electrodes require no special description under control conditions the configuration depended primarily on the direction of conduction with respect to the bipolar recording electrodes (see Figs 2 6) Complexes recorded from the epicardium of the right and left atrial appendages have been designated A_1 and A_2 and those recorded from the epicardial surface of the ventricles by V Three major components usually were recorded through the electrodes located over the bundle of His The first represented activity in the atrium in the vicinity of the electrode (A_3) the second activity in the bundle of His (H) and the third activity in the underlying interventricular septum (S or S) Records from either the bundle branches or the Purkinje papillary junctions consisted of two major deflections the first represented

Table III *Conduction times—45 minutes of ischemia*

	Control	Ischemia (min)										Perfusion (min)							
7 8/59		1	3	4	5	7	10	15	25	35	45	1	5		14	17	2	27	32
A_1 H	19	20	4	D	D	D	—	—	—	—	—	—	—	D e	—	—	143R	200	85
A_2-H	35	40	61	D	D	D	—	—	—	—	—	—	—	f b	B	65	—	—	49
H RPPJ	19	19	18	70	F							F	F	i	D	D	B	B	44
RLPJ RV	25	21	23	29	F							F	F	l t	V	V	V	V	30
H S	8	0	68	83	F ⟶							F	F	d	D	D	152	12[illegible]	83
P PM	20	17	16	16	F							F	F		V	V	V	V	15

Additional [illegible] RV Right [illegible] B [illegible]

Table IX. Conduction times: 120 minutes with 50 per cent nitrogen in oxygenator

	Control	Hypoxia (min.)										Oxygenation (min.)				
	10 & 30	1	3	7	15	30	45	60	90	105	120	1	5	10	21	26
A H	28	1	31	4R	29	26R	28	R	R	35	35	31	33	33	35	35
A H	26	21	24	13R	[illegible]	3 R	3	R	R	29	29	29	5	28	30	28
H RBB	18	16	17	18	17	1	13	15	15	16	19	18	18	16	15	15
H LV	53	51	5	54	51	51	46	45	49	31	35	53	51	50	46	45
H S	0	64	64	63	65	60	59	57	59	65	65	65	61	63	60	5
E M	2	5	23	4	18	18	15	15	15	17	1	17	1	17	17	16

Hypo ... pe ... 33 ... 50 per ... 150 per ce ... dual ... 120 m ... after

activity in the specialized conducting tissue (B or P) and the second, activation of the underlying septum (S) or papillary muscle (M).

Over three thousand intervals between the various components of the electrograms were measured and expressed as conduction time in milliseconds. Average values are recorded in condensed form in Tables I-VI. Changes in conduction time and in electrical activity of the conducting system were studied prior to and during ischemia and hypoxia and also after a period of recovery. Although the experimental error was well below 10 per cent, only a change greater than 10 per cent in the conduction time was considered to be significant. The results are presented in two parts: (A) those obtained during ischemia and (B) those obtained during hypoxia.

A. Ischemia: Ventricular fibrillation occurred in all experiments within 5 to 13 minutes after cross clamping of the aorta. The atrium did not fibrillate at any time. The onset of fibrillation frequently was preceded by runs of retrograde conduction or ectopic activity which originated in the bundle branches or Purkinje system. After the aorta was unclamped, defibrillation was accomplished with one or two countershocks of 60 to 110 volts and 0.1 second duration.

Results of experiments in which ischemia lasted for periods of 15, 30 and 45 minutes are given in Tables I-III; representative electrograms for each type of experiment are shown in Figs. 2-4. During ischemia which lasted 15 minutes the earliest change noted was a progressive increase in the interval between activity in the atrium and that in the bundle of His (A-H), representing slower conduction in the atrioventricular node. At the same time there was a gradual decrease in the amplitude, widening, and slurring of the atrial electrogram. This complex became indistinct in 4 to 5 minutes (Fig. 2 and Table I). Conduction time from the bundle of His to the bundle branch (H-LBB) or to the Purkinje system remained essentially unchanged until the onset of fibrillation after 6 to 12 minutes of ischemia. Electrical activity in the bundle of His, bundle branches and Purkinje fibers continued during fibrillation and until the end of the ischemic period, although the electrographic complexes were diminished in amplitude in some experiments, propagated activity could be recognized. Conduction time between the bundle branch and the epicardial surfaces of the corresponding ventricle (LBB-LV) began to prolong after 3 to 5 minutes of ischemia and continued to increase until the onset of fibrillation. Even in the absence of fibrillation, electrical activity of the ventricular myocardium was difficult to identify in epicardial electrograms after 10 minutes of ischemia. There was a considerable increase in the interval between activity in the bundle of His and the activation of the underlying septum (H-S) and a slight increase in the interval between activity of the bundle branch and that of the underlying septum (LBB-S_1). Activity in the septum also became indistinct after 10 minutes of ischemia.

During ischemia which lasted 30 minutes the changes were similar to those described above (Fig. 3 and Table II). In the particular experiment shown in Fig. 3 the atrial electrogram gradually diminished in amplitude during the first 10 minutes

and then gradually increased during the remainder of the ischemic period while the ventricles were fibrillating. Activity in the bundle of His became indistinct after 20 minutes whereas activity in the Purkinje system continued throughout the ischemic period.

Ischemia which lasted 45 minutes produced no changes in conduction different from those described. Activity at the right Purkinje papillary junction could be identified until after 35 minutes; all electrical activity was absent after 40 minutes of ischemia (Fig 4 and Table III).

After periods of ischemia which lasted 15 and 30 minutes had been followed by a period of recovery there was a persistent prolongation of the conduction time from atrium to bundle of His (A H and A_f-H); other conduction times returned to the control values (Figs 2 and 3 and Tables I and II). When the period of ischemia was extended to 45 minutes a persistent prolongation of conduction time from the bundle of His to the Purkinje system (H RPPJ) resulted. A slight persistent prolongation of the conduction time between the Purkinje system and the ventricular epicardium (RPPJ RV) and the interval between the bundle of His and the septal myocardium (H S) was recorded (Fig 4 and Table III). During the recovery period in this experiment there was a transient 2 1 block between the atrium and the bundle of His and also dissociation between the bundle of His and the peripheral Purkinje system.

The aorta was cross clamped for an additional 15 minutes in the experiment of May 29 1959 (Fig 4) in order to compare the effects of a single 30 minute period of ischemia with those caused by two successive 15 minute periods. The additional 15 minutes of ischemia resulted in a further prolongation of the conduction time between the atrium and the bundle of His (A-H) and a prolongation of the interval between the bundle of His and the bundle branch (H LBB) which persisted after defibrillation and an 18 minute period of recovery. The latter change did not occur after single periods of ischemia which lasted 30 minutes. After 45 minutes of ischemia

Table V Conduction times—60 minutes with 100 per cent nitrogen in oxygenator

	Control	Hypoxia (min)													Oxygenation (min)					
3 2 60		1	3	4	5	8	10	1	30	35	40	45	55	60	5	10	1	20	40	60
V A	16	15	15	15	14	14	R	R	R	8	—	—	—	—	—	—	16	18	17	18
V V	19	15	19	18	16	16	R	R	R	78	—	—	—	—	—	—	15	16	12	3
V H	56	33	32	35	33	59	R	R	R	46	—	—	—		—	—	D	82	79	70
A-H	37	36	35	37	37	40	R	R	R	73	—	—	—	—	—	—	D	67	68	67
H RPPJ	75	3	26	26	26	23	29	36	26	25	25	E	F	E	30	5	23	23	28	25
RPPJ RV	35	35	35	35	34	34	32	31	30	31	33	E	E	E	6	61	59	58	48	50
H LV	63	65	66	66	64	63	66	71	57	5	56	E	F	E	68	65	60	60	60	58
H S	83	84	86	87	83	84	87	90	74	69	73	E	F	E	92	89	86	83	87	77
P PM	19	31	22	24	22	72	22	19	24	25	29	E	F	E	43	41	38	36	76	28

Hypoxia was prod ed by 100 per ce nt g dm ed f 60 minutes E Ectop be

Table VI Conduction times—120 minutes with 100 per cent nitrogen in oxygenator

	Control	Hypoxia (min)													Oxygenation (min)					
10 13 59		5	10	13	24	34	44	54	64	74	84	94	104	120	5	10	15	21	42	52
V H	27	34	23	54R	D								—	—	D					
A-H	41	39	36	24R	D								—	—	D					
H RPPJ	19	18	19	19	18	20	20	18	9R	25	5	19	31	30	25	31	31	31	30	35
H LV	53	53	54	52	52	49	50	52	50	48	43	44	46	48	48	53	50	52	50	50
H S	84	83	76	78	68	69	68	69	40	68	70	71	75	70	84	83	80	83	88	[illegible]
P IM	31	31	29	29	27	30	30	8	28	32	33	25	27	28	21	17	15	36	36	

Hypoxia was prod ced by 100 pe ce ks g adm [illegible] tes

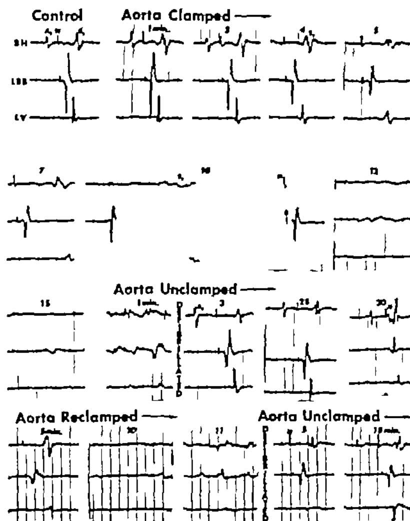


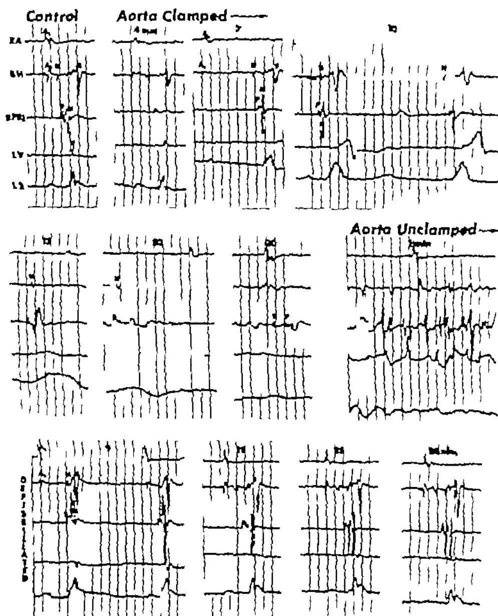
Fig. 2. Electrograms obtained at the indicated times during two successive 15 minute periods of ischemia, each followed by a period of recovery. The electrodes are positioned as follows: bundle of His (*BH*), left bundle branch (*LBB*), and left ventricle (*LV*). The components of the electrograms are labeled as follows: *A*, right atrium; *H*, bundle of His; S_1, septum near bundle of His; *B*, bundle branch; *S*, septum near bundle branch; and *V*, ventricle. Note retrograde conduction from the bundle branch to the bundle of His followed by a normal sequence after 10 minutes of ischemia and ventricular fibrillation beginning after 12 minutes of the first ischemic period. In this and all subsequent records the time lines indicate intervals of 40 msec.

the aorta was cross-clamped for an additional 60 minutes. After defibrillation and 30 minutes of recovery there was no return of atrial activity and appreciable prolongation of all conduction times persisted.

During the time that the aorta was cross-clamped the temperature of the ventricular endocardial surfaces fell from 33°-36°C. to 30°-33°C. in 10 to 15 minutes and remained at this level until coronary perfusion was resumed. This change in temperature was not thought to make any important contribution to the disturbances of conduction described (unpublished observation of Stuckey and Bagdonas).

B. Hypoxia.—Results obtained during 120 minutes of hypoxia which was produced by using a mixture of 50 per cent nitrogen and 50 per cent oxygen in the oxygenator are shown in Table IV; representative electrograms are shown in Fig. 5. Fifteen minutes after the start of the 50 per cent nitrogen mixture the arterial oxygen saturation was 55 to 46 volumes per cent and remained in

this range until the end of the hypoxic period. The conduction time from the right atrium near the sinoatrial node to the bundle of His (A_1H) increased while the atrium His interval recorded from the electrode located over the bundle of His (A_2H) remained essentially unchanged. This suggested a slowing of conduction in the right atrium. The gradual shortening of the Purkinje–papillary muscle interval (P PM) observed during the initial 15 minutes was thought to be due to recovery from injury



F 3 Electrograms obtained at the indicated times during 30 minutes of ischemia and during subsequent period of recovery. Electrodes in addition to those used for Fig. 2 are positioned as follows: right atrium near S-A node (*RA*) and right Purkinje papillary junction (*RPPJ*). *L₂* designates Lead II of a standard electrocardiogram. Components of the electrograms not identified in Fig. 2 are labeled as follows: *1*, right atrium near S-A node; *S*, septum near bundle of H; *M*, right anterior papillary muscle; and *P*, activity in the Purkinje fiber. Note retrograde conduction between the bundle of His and Purkinje fibers at 10 minutes and ventricular fibrillation at 13 minutes. Note the persistence of Purkinje activity at 30 minutes.

caused during placement of the electrode. The transient shortening of all the conduction times in the conducting system below the atrium observed at 45 minutes resulted from a temporary rise of 1.5°C. in the temperature of the body. In general, there was very little change in the conduction system during 120 minutes of moderate hypoxia. After reoxygenation, prolongation of the A_1-H conduction time persisted. The shortening of the conduction times measured in the remainder of the conducting system after 26 minutes of reoxygenation also resulted from a temporary slight rise in the temperature of the body. Left ventricular contractions monitored with a strain gauge arch decreased to from one fourth to one third of the control amplitude during hy-

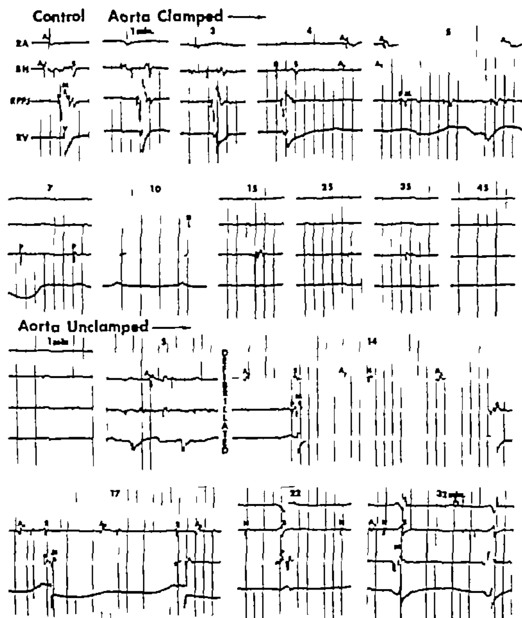


Fig. 4. Electrograms obtained at the indicated times during 45 minutes of ischemia and during subsequent period of recovery. *RV*, Right ventricle. Note ventricular fibrillation at 5 minutes. Activity of the bundle of His persists until 15 minutes of ischemia and activity at the Purkinje-papillary junction until 35 minutes. During the recovery period note the atrium-His block (2:1) and His-Purkinje dissociation at 14 minutes and normal atrium-H conduction and continued His-Purkinje dissociation at 17 minutes.

poxia and persisted at this level after reoxygenation

When oxygen was excluded from the oxygenator with 100 per cent nitrogen the arterial oxygen saturation fell to 16.4 volumes per cent within 30 minutes and remained in this range during the remainder of the hypoxic period *During hypoxia* which lasted 60 minutes (Fig 6 Table V) electrical activity of the atrium gradually diminished and a nodal or His rhythm developed at 10 minutes The retrograde activation of the atrium during nodal rhythm is indicated by the reversal of the sequence of the atrial complexes (A A and A) After 35 minutes of hypoxia no clearly recognizable atrial activity was recorded From 45 minutes *until the end of the hypoxic* period the pacemaker site probably was located in the left bundle branch or in

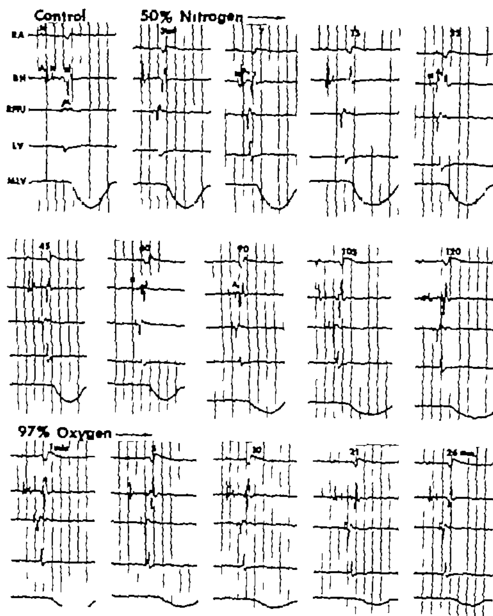


Fig. 4 Electrogram obtained at the indicated times during 170 minutes of moderate hypoxia with 90 per cent nitrogen and 50 per cent oxygen in the oxygenator and during a subsequent period of recovery *MLV* Myogram recorded from the left ventricle Note the nodal or His rhythm at 7 25 60 and 90 minutes of hypoxia

the Purkinje system Electrical activity in the specialized conducting system and in the ventricles continued until the end of the period of hypoxia although the amplitude of the complexes was somewhat diminished After 60 minutes of reoxygenation there was a persistent prolongation of intervals between atrium and bundle of His (A_1-H and A-H) and conduction from the Purkinje system to ventricular epicardium (RPJ-RV) and from Purkinje system to papillary muscle (P-PM) was delayed

Severe hypoxia which lasted 120 minutes produced no additional changes In this experiment electrical activity of the atrium persisted through 99 minutes (Table VI) Conduction in the infra-atrial portions of the conducting system was not markedly affected during the entire hypoxic period After reoxygenation atrium-His dissoci

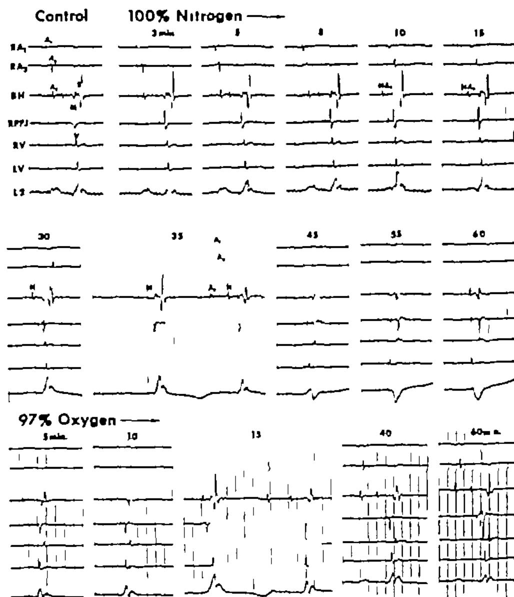


Fig 6 Electrograms obtained at the indicated times during 60 minutes of severe hypoxia with 100 per cent nitrogen in the oxygenator and during a subsequent period of recovery Additional electrodes are right atrium near S-A node (*RA*) and right atrium 2 cm from S-A node (*RA*) *A* Activity at right atrium 2 cm from S-A node At the 35 minute interval note an ectopic beat probably originating in Purkinje fiber followed by a normal beat Early activation of the left ventricle at 45 through 60 minutes of hypoxia is probably due to an ectopic pacemaker in the left bundle branch or in the Purkinje fibers within the left ventricle

ation persisted and the conduction time from the bundle of His to the Purkinje system (H-RPPJ) became persistently prolonged. The Purkinje–papillary muscle interval (P-PM) was somewhat variable but appeared to shorten.

Discussion

Interpretation of the records obtained with the technique used in the present experiments has been discussed in previous publications.[7, 11] Since interelectrode distances remained constant, the conduction times between electrodes implanted along the major conduction pathways were inversely related to the average conduction velocity. However, intervals designated by the A-H, LBB-S, and P-PM, which are recorded from a single electrode, represent differences in the time of activation of the underlying tissues and thus are not conduction times. In experiments of this type the possibility of injury to underlying tissue by the electrodes must always be considered. The presence of the chronically implanted electrodes has not significantly affected either conduction through the bundle of His and the Purkinje system or the electrocardiogram during periods of observation which lasted up to 2 months (unpublished observation). In numerous experiments in which this technique is used and which last 3 to 6 hours, no significant change in conduction has been observed. One other source of experimental variation in conduction velocity must be considered and this is the fall of 3 to 4° C. in the temperature of the heart incident to cross-clamping of the aorta. This drop in temperature is not considered to be of significance in producing any of the major changes observed during ischemia. This statement is based on experiments in progress on the effects of hypothermia on conduction in the specialized system. Observations made during recovery from ischemia may reflect changes due to the defibrillation which was necessary in each experiment. However, other studies[14] have shown that defibrillation by the method used in these experiments has little effect on cardiac excitability.

The interval between atrial activity recorded at the electrode over the bundle of His and activity in the bundle of His (A_1-H) is thought to be largely a measure of conduction through the atrioventricular (A-V) node and proximal bundle of His. Other studies have shown that all portions of the atrium in the vicinity of the A-V node and the bundle of His are normally activated within an interval of 5 to 10 msec.[1] If no slowing of conduction in the A-V node were present, activity in the adjacent atrium and the bundle of His would be expected to occur almost simultaneously. The fact that activity in the bundle of His occurs 35 to 60 msec. after local atrial activity (A_1) suggests that these records actually indicate the magnitude of A-V nodal delay. This interpretation suggests that the A-V node is the portion of the conducting system most sensitive to ischemia, since it was the first to be affected and the most susceptible to irreversible change.

Records of atrial activity exhibited considerable variation in conduction times and in the sequence of activation. This probably was due to shifting of the atrial pacemaker during the course of the experiment and consequent changes in conduction pathways. In a number of experiments there was an increase in the conduction times between several electrode sites on the atrium. This, together with the fact that the amplitude of the atrial electrogram was depressed, indicates a slowing of atrial conduction during both ischemia and hypoxia.

Conduction between the Purkinje system and the ventricular epicardium (RPPJ-RV) and between the Purkinje system and the septal endocardium (LBB-S_1 and P-PM) also was quite sensitive to ischemia. However, there was no irreversible prolongation of these conduction times after ischemia which lasted as long as 45 minutes. The specialized conducting system per se, exclusive of the A-V node, was relatively resistant to ischemia, and the peripheral Purkinje system was most resistant, since it continued to fire throughout 40 minutes of ischemia and at a time when all other electrical activity had ceased.

During hypoxia the atrium and A-V node again were the most sensitive portions of the heart and specialized conducting system. When the heart was subjected to severe hypoxia for 120 minutes with arterial oxygen saturations as low as 4 per cent, the infra-atrial portion of the conduction s-

tem was not markedly affected These observations are consistent with physiologic studies on isolated mammalian heart tissue during deprivation of oxygen

One of the obvious differences between the effects of ischemia and those of hypoxia on cardiac conduction is that ventricular fibrillation regularly occurred with ischemia and never with hypoxia Furthermore recorded electrical activity was completely abolished by 45 minutes of ischemia whereas with the exception of the atrium electrical activity was not remarkably affected by 120 minutes of severe hypoxia This would suggest that a lack of oxygen alone may not be the most important factor in the production of changes observed during ischemia Other factors such as retained metabolites and changes in blood pH and electrolyte concentrations may be of greater significance in affecting the conducting system This problem is the subject of further study

Summary

Close bipolar electrodes have been attached at selected locations on the epicardium and endocardium of in situ canine hearts during total cardiopulmonary bypass Records from various parts of the atrium specialized conducting system and ventricle have been obtained during ischemia and severe hypoxia Atrial and A V nodal conduction were the most sensitive to ischemia and hypoxia The specialized conducting system was least affected by ischemia and the peripheral Purkinje system was the most resistant Ventricular fibrillation occurred in all experiments during ischemia but was not produced by hypoxia Recordable electrical activity was abolished after 40 minutes of ischemia During 120 minutes of severe hypoxia electrical activity in the atrium was depressed whereas that in the specialized conducting system distal to the A V node was not markedly affected

In view of the striking differences between the effects of ischemia and hypoxia on the specialized conducting system distal to the A V node it is concluded that a lack of oxygen may not be so important as other factors such as the retention of metabolites and changes in blood pH and electrolyte concentrations which occur during ischemia

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REFERENCES

1 Colla F nd Nelso I A Ancuet ler nce f beating and resting heart d rin perf sion t arious temperature Proc Soc Exper Biol & Med 9 185 195
2 Wesolow ki S Fisher J F news) J Cerbales R nd Welch C Recovery f the *dog heart fter carying periods of acut* ischemia S Forum 3 0 195
3 Kardesch M Hoc nc mp C and B ng R The effect of complet schemia on the tra cellula lectrical act ity of the whole m m mal heart Circul tion Res 6 15 1958
4 Trautwei W Gott tei l nd Dudel J Der Akt on strom d M kardfas m Sauerstoffmangel Pflug rs Archi ges Phys ol 260 40 1954
5 Coraboeuf E C rgoud Y M Lapl ud J nd D splaces A Action de l noxie su les potentiels électrique des cellules cardiaques de mammif res actives isolé (t u tricul ure isolé de Coba e) Compt rendu Acad Sci (Paris) 216 3100 1958
6 Allen J G F tracorpo eal circul tion Springfield Ill 1958 Charles C Thom p 69
7 Hoffm B F C nefield I F Stuckey J H nd Bagdon A A Electrical acti t during the I R t ss l Circulation Res (In press)
8 Stuckey J H Hoffm B F Sak C I Kottmeier I K and Fabbone H Electrode identification of the conduct on system during open heart urgery S Forum 9 20 1959
9 Stuckey J H Hoffman B F Amer N S Cranefield I F C ppellett R R and Domingo R T Localization of the bundle of His w th rfa el ctrode during cardiot omy S Forum 10 551 1960
10 Amer N S Stuckey J H *Hoffman B F* Cappelletti R R and Domingo R T Act tion of the terventricular septal myocardium studied luring cardiopulmonary by pass Am H rt J 59 2 4 1960
11 Hoffman B F Cranefield I F Stuckey J H Ame N S Cappelletti R R and Domingo R T Direct measurement of con duction elocity in in situ specialized conduction system of mammalian heart Proc Soc Exper Biol & Med 102 55 1959
12 Pires de Carvalho A nd de Almeida D F The pread of activ ty thro ugh the trioventric ula node Circulation Res (In press)
13 Webb J I and Hollander I B Metabolic pects of the rel tionship bet een the con tractil ty nd membrane potentials of the rat trium Circulation Res 4 618 1956
14 Hoffma B F Suckling E F and Brooks C McC A Inexcitabilty of dog entricle nd ef fects of defibrillation Circ Res 3 147 1955

Blood flow in the calf of the leg after running

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Much is now known of the effect of standardized muscular exercise on the flow of blood in skeletal muscle in man both during and after contraction This was first described by Gaskell and later by Grant Barcroft and Dornhorst Imig and associates and many others

Recently Black has carried out experiments after more normal forms of exercise such as walking or running in which he observed the behavior of the flow of blood in the calf by means of venous occlusion plethysmography In these experiments the subjects walked or ran round a very short track 31 yards (28 35 meters) in circumference and maintained a standard step of 2 feet and 9 inches (83 8 cm) by following marker lines painted on the laboratory floor At any speed the total distance did not exceed 130 yards (118 87 M) Within a low range of speeds (below 3 5 miles per hour 5 6 kilometers per hour) the flow obtained immediately on cessation of exercise (peak flow) was directly related to the speed at which the exercise was taken but the blood debt repayment was not affected by speed However within a higher range of speed (above 3 5 m p h) the peak flow did not increase with the speed of walking whereas the postexercise hyperemia did From this evidence he concluded that vessels were capable of dilating sufficiently to meet metabolic demands during exercise up to a speed of about 3 5 m p h He suggested that at this speed the dilatation of the vessels reached a maximum and so at speeds above this a build up of metabolites occurred which resulted in a correspondingly larger postexercise hyperemia

If this interpretation is correct it follows that the blood-debt in the calf caused by running at speeds greater than 3 5 m p h will increase as the distance run increases If this occurs under all conditions it is difficult to see how an athlete can run a marathon race without incurring an enormous blood-debt which might take hours or even days to repay

In the present experiments an attempt has been made to investigate this problem by studying the postexercise hyperemia in the calf of trained and untrained subjects after they had run distances which varied from 220 yards (201 2 M) to 8 miles (12 9 km) under natural conditions on an outdoor track

Methods

Eight healthy male students all between the ages of 19 and 25 years acted as subjects in this series of experiments Four of these subjects were relatively untrained in running and 4 were prominent members of the University Athletic Club The degree of physical fitness in the untrained subjects was fairly uniform and not abnormally high e g S H had not

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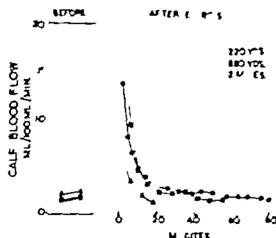


Fig. 1. Flow of blood in calf of one untrained subject during control periods and after he had run 220 yards, 880 yards, and 2 miles at 8.5 m.p.h.

taken part in any sporting activity for some time, was of a rather studious nature and traveled each day by bus. The athletes, on the other hand, were in the middle of their season and extremely fit.

Each subject was asked to run distances of 220 yards (201.2 M.), 880 yards (804.7 M.), and 2 miles (3.2 Km.) (on separate occasions), and each run was repeated once, so that each subject carried out six runs. The speed of the whole group was regulated to the speed which the untrained subjects could maintain over a distance of 2 miles without undue physical stress. This was found to be 8.5 m.p.h. (13.7 Km. per hour), and this speed was maintained over all distances during the experiments. In two additional experiments observations were made on 2 trained subjects who ran distances of 6 miles (9.7 Km.) and 8 miles (12.9 Km.) at the same speed.

The subject wore singlet, shorts, socks, and running shoes, and the running was done on an outdoor circuit 300 yards (274.3 M.) long. This was marked out in thirds, and the time at which the runner should be at each of the three points was calculated in advance. If the subject was running either too quickly or too slowly, the observer could instruct him to slow down or speed up by a prearranged system of blasts on a whistle.

The weather conditions and temperature were noted on each occasion, and the room temperature was maintained at 20 to 21° C.

Blood flows were recorded by venous occlusion plethysmography by means of a temperature-controlled water-filled plethysmograph[4] which was maintained at 34° C. throughout the experiment.

Since speed in obtaining the first recording after the cessation of exercise is essential, it was necessary to use a quick method of filling the inner jacket of the plethysmograph. To do this, a reservoir was prepared above the level of the bead with an emptying tube placed in the chimney of the plethysmograph. As soon as the subject placed his calf in the plethysmograph, the tap was opened and the inner jacket allowed to fill while one person placed a pneumatic cuff around the ankle and a second person a collecting cuff just below the knee. The plethysmograph was then connected up to the recording apparatus, and usually the first recording was obtained within 1½ to 2 minutes after exercise.

Procedure. For some time before the experiment the subject had taken as little exercise as possible. On arriving at the laboratory, he lay down on a couch for a period of 30 to 45 minutes. At the end of this time, two series of blood flows were taken about 10 minutes apart (10 flows in each). The average of these was taken to be the resting flow. The subject then removed his calf from the plethysmograph and began running round a circuit for the appropriate distance. The run ended at the laboratory couch, where he removed his left shoe and sock as quickly as possi-

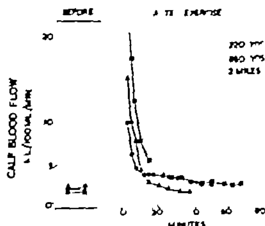


Fig. 2. Flow of blood in calf of one trained subject during control periods and after he had run 220 yards, 880 yards, and 2 miles at 8.5 m.p.h.

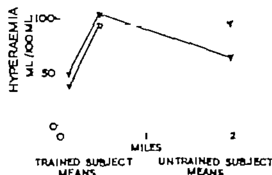


Fig 3 Mean blood debt repayments in trained and untrained subjects after they had run 220 yard 880 yards and 2 miles

ble and placed his left calf in the plethysmograph Groups of five blood flows were taken with 1 minute intervals separating the first three then a 3 minute interval separating the third from the fourth and subsequently the groups of flows were separated by 4 minute intervals The experiment was continued until the flow of blood was considered to have returned to normal as indicated by the plethysmograms

The mean of each group of five flows was calculated and plotted on a graph against time after cessation of exercise The area under this curve represents the total amount of blood flowing through the calf during the period of observation The hyperemia which resulted from the exercise is then the amount of blood flowing through the calf during this period in excess of the normal flow which can be calculated by means of the resting values obtained at the beginning of the experiment This value is referred to as the blood debt repayment

Results

Fig 1 shows the pattern of postexercise flows in one untrained subject after he had run 220 yards 880 yards and 2 miles at 8 5 m p h In all cases there was a marked postexercise hyperemia which persisted for some time after exercise had ceased The peak blood flow reading obtained 2 minutes after the running ended showed after 220 yards a fourfold increase over the resting flow after 880 yards an elev fold increase and after 2 miles an eight fold increase The hyperemias following the three distances lasted 25 55 and 80 minutes respectively The total blood debt repayment after the subject had run 220 yards was 20 ml after 880 yards it was 114 ml and after 2 miles it was 129 5 ml

Fig 2 shows the effect of running the same three distances on the flow of blood in the calf of a trained runner The repayment after the 220 yard run was again much less than that after the 880 yard run but in this case the repayment after the 2 mile run was only one half of that after 880 yards

Tables I and II list the repayment values for all six runs in each of the 8 subjects There was a considerable variation in the responses to the same stimulus from person to person and indeed in the same individual from time to time e g in M M the repayments after he ran 220 and 880 yards were not appreciably different on one occasion whereas on a second occasion the repayment after he ran 880 yards was three times greater than after 220 yards

In Fig 3 the mean repayments after the running of each distance have been plotted for the group of untrained runners and also for the group of trained runners It can be seen that in the untrained subjects the mean repayment increased with

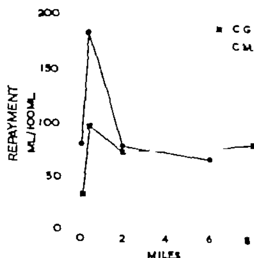


Fig 4 Blood-debt repayments in trained bjects after they had run 6 and 8 miles The repaymen after the 220 yard 880- ard nd 2 mile run lso hown for each subject.

Table I. Blood-debt repayments in 4 untrained subjects after a run of 220 yards, 880 yards, and 2 miles

Subject	Blood-debt repayment (ml./100 ml.) 220 yd.	880 yd.	2 mile
J.H. (1)	20	93	93
J.H. (2)	70	110	129
J.D. (1)	55	95	106
J.D. ( )	3	85	97
M.M. (1)	4	55	100
M.M. ( )	42	121	68
S.H. (1)	25	95	95
S.H. (2)	3	98	64
Mean	39	94	94

Table II. Blood-debt repayments in the trained subjects after a run of 220 yards, 880 yards, and 2 miles

Subject	Blood-debt repayment (ml./100 ml.) 220 yd.	880 yd.	2 miles
M.C. (1)	31	37	45
M.C. (2)	20	23	68
C.M. (1)	80	182	78
C.M. (2)	56	147	74
C.G. (1)	34	96	3
C.G. (2)	40	5	40
J.D.P. (1)	9	114	72
J.D.P. (2)	5	150	69
Mean	50	104	65

distance up to 880 yards, but no further increase in repayment occurred when the distance was increased to 2 miles. In the trained subjects the mean debt repayment increased with distance up to 880 yards as before, but an increase in the distance to 2 miles resulted in a drop in repayment to near the value obtained after a run of 220 yards. A statistical analysis of all the results showed that in the untrained group the repayments after 220 yards were significantly less than those after 880 yards or 2 miles ($p < 0.01$), but the difference between the debts incurred by running the latter two distances was not statistically significant at the $p < 0.01$ level. In the case of the trained group the repayments after the 880 yard run, as in the untrained group, were significantly greater than those after the 220-yard run ($p < 0.01$). However, the repayments after the 2 mile run were significantly smaller than those after the 880 yard run ($p < 0.01$). The difference between the repayments after the 220 yards and the 2 miles was not statistically significant at the $p < 0.01$ level.

Fig. 4 shows the repayments measured after one trained subject ran 6 miles and another ran 8 miles, together with the repayments measured for each after the shorter distances. It can be seen that no appreciable increase in repayment occurred with this greatly increased distance; in fact, C. M. showed a slight decrease in repayment after running 6 miles.

Discussion

There is good evidence that postexercise hyperemia is caused, either directly or through an axon reflex, by the action of metabolite(s) formed during contraction on the blood vessel of muscle.

In the present experiments the calculated blood-debt repayment values after exercise probably included an increase in the flow of blood through the skin of the calf, since the form of exercise used caused a considerable amount of general body heating. In some subjects in whom the temperature of the mouth was recorded before and after exercise, it was found that the temperature of the body was raised by up to 1.7° C. after the 2 mile run, and occasionally it was raised by up to 0.5° C. after the 880 yard run. One would expect the extent of the skin contribution to the hyperemia to be modified by the outdoor temperature on the occasion of the experiment, and so a record of the outdoor temperature during each run was kept. However, a comparison of the change in temperature and the variation in hyperemic response from day to day did not reveal any obvious relationship.

The results of the experiments on the trained and untrained subjects show clearly that when the subjects were running at 8.5 m.p.h. the blood flow repayments did not increase with distance after a critical distance had been exceeded. Indeed, in the trained runners there was a marked fall in repayment above a distance of 880 yards. This is supported by the results of the additional experiments with trained subjects, when one ran a distance of 8 miles and the other ran 6 miles. These show clearly that after 880 yards has been

exceeded distances up to 8 miles can be run without any appreciable increase in repayment It can be concluded from these results that while the subject is running at this speed vasodilatation in the muscle can satisfy the increased metabolic requirements so that a state of equilibrium is reached at which the rate of removal of metabolite by the blood stream can keep pace with its rate of formation in the muscle In trained subjects in particular it has been noted that the repayment after 2 miles is considerably less than after 880 yards This could indicate an increased mechanical efficiency in the trained runner over the longer distance or it could indicate an improved supply of blood to his calf muscle but any attempt to produce a definite explanation of this fact on the data available would be unjustified

A comparison of results obtained here with those obtained for walking[1] is of interest in an evaluation of the relative costs of walking and running with respect to the calf muscle In Fig 5 are plotted the mean postexercise repayments after walks of 880 yards and 2 miles at speeds of 3 m p h (4 8 km per hour) and 5 m p h (8 1 km per hour) and also those after the running of these distances at 8 5 m p h The most striking feature of this diagram is that although in walking at 5 m p h there is a progressive build up of debt with distance no such accumulation occurs during running at a much faster speed this difference suggests that the amount of work done by the calf muscle is less in running than in walking although in running the over all exhaustion of the body may be greater This is borne out by these results since it is clear from the diagram that the cost of running 880 yards at 8 5 m p h correspond to the cost of walking this distance at only 5 m p h and the cost of running 2 miles at 8 5 m p h is the same as that of walking 2 miles at between 3 and 5 m p h So although it has been found that running at this speed does not cause any progressive build up of metabolites running at a greater speed if this were practicable might lead to the metabolic requirements of the tissues outstripping the increase in the flow of blood in the calf so that accumulation of metabolites might occur

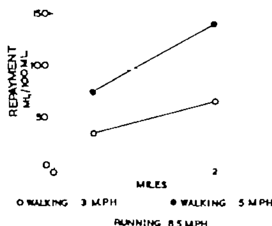


Fig 5 Blood-debt repayments in the calf after walks of 880 yard and 2 miles at speeds of 3 m p h and 5 m p h are shown along with those after the running of these distances at 8 5 m p h The blood debt repayment values after the walks are taken from the results of Halliday

Summary

1 Measurements were made of the blood debt repayments in the calf of 4 untrained subjects after they had run each of three distances 220 yards 880 yards and 2 miles at a constant speed of 8 5 m p h under natural conditions on an open air track Similar observations were made in a group of 4 athletes

2 A marked postexercise hyperemia occurred in both groups of subjects after all distances

3 In the untrained subjects blood debt repayment increased with distance up to 880 yards and remained constant with further increase in distance

4 In trained subjects the blood-debt repayment also increased with distance up to 880 yards but after 2 miles it dropped to a level significantly lower than that after 880 yards

5 Blood debt repayments are similar after a run of 880 yards at 8 5 m p h and after a walk of the same distance at 5 m p h

6 It is concluded that at this speed of running there is no progressive build up of metabolite either in trained or untrained subjects although this does not exclude the possibility of such a build up occurring at greater speeds

The author wishes to thank Professor A D M Greenfield who suggested this problem

I C Roddie for his help and ad ice Thanks are also due to Mr S J Kilpatrick of the Department of Social nd Preventive Medicine for his help in the stati tical evaluation of the d ta

REFERENCES

1 Gaskell W H On the changes of the blood treum muscles through stimulation of their nerves J An t Lond 11:360 1877
2 Grant R T Observ tions on the blood circul tion oluntary muscles in ma Clin Sc 3 157 1938
3 Barcroft H and D rnhorst A C Blood flow through the human calf during rhythmic exercise J Physiol 109:40 1949
4 Imig C J B uer \ nd H milton G F Effect of exercise on blood flow through the forearm and calf of human subjects Am J Physiol 187:607 1956
5 Black J E Blood flow requirements of the calf m cles after walking and running Clin Sc 18:88 1959
6 Greenfield A D M A simple water filled plethysmograph for the hand or forearm with temperature control J Physiol 123:62P 1954
7 Anrep G V and von Saalfeld F Blood flow through the skeletal muscle in relation t its contraction J Physiol 85 375 1835
8 Hilton S M Experiments on the postcontraction hyperemia of skelet l muscle J Physiol 120:230 1953
9 Halliday J A Blood flow in the human calf after prolonged walking Am Heart J 60 110 1960

The effect of citrate infusion on the electrocardiogram of the hypothermic and normothermic dog

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The effects of hypothermia on the electrocardiogram (ECG) have been adequately described in the literature (Osborn Hicks and associates Emslie Smith[1]) however the effects of citrate infusion alone in hypothermic and normothermic animals and in man have received little attention Argent[4] suggested citrate toxicity was responsible for ventricular fibrillation after massive transfusion in a human being Ludbrook and Wynn[6] reported ECG findings of Q T prolongation ST T changes atrial asystole and ventricular fibrillation in a patient who received a large quantity of citrated blood during hypothermia

The present study was undertaken (1) to discover any characteristic changes in the ECG due to infusion of citrate (2) to attempt correlation of these changes with the level of citrate in the blood and (3) to ascertain the effect of hypothermia on these changes

Methods

Twelve mongrel dogs were used Each animal received acid dextrose citrate (ACD) solution buffered with sodium hydroxide to pH 7 4 at normal body temperature About 2 to 3 weeks later hypothermia was induced by immersion of the animal in cracked ice to a rectal temperature of about 29° C and the infusion with ACD solution was repeated An attempt was made to have the rectal temperature stabilized before the experiment was begun All animals were anesthetized with thiamylal sodium and were given positive pressure artificial respiration with room air while they were hypothermic

The rate of infusion was determined by the weight of the animal Infusion was given at a rate of 3 45 mg /Kg /minute a volume of 0 3 ml per Kg /minute (7 5 ml /Kg or 112 5 ml total for a dog which weighed 15 kilograms) A volume of about 100 ml of blood was withdrawn during the experiment for chemical analyses

Specimens of blood were obtained from the inferior vena cava via a polyethylene catheter passed into the femoral vein and arterial pressures were recorded through a similar catheter placed in the femoral artery Recordings were performed with a Sanborn Poly Viso 150 M recorder equipped with a Statham P23B strain gauge for determinations of pressure the base line was adjusted to heart level Standard electrocardiographic Leads II and III and ar

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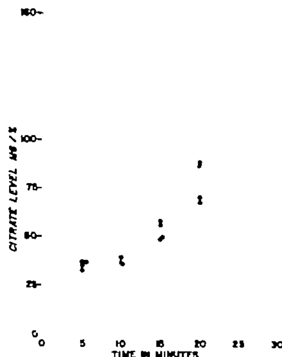


Fig. 1. Levels of citrate in the blood during normothermia and hypothermia. Solid circles represent levels of citrate in hypothermic animals and open circles those in normothermic animals. Rate of infusion was constant during all experiments. Note uniformly higher figures obtained with hypothermia.

terial pressure (25 mm./sec. paper speed) were recorded at the same time that blood was being obtained for analysis. A control observation was made before each experiment and specimens were obtained and recordings were made every 5 minutes for 25 minutes during infusion of the ACD solution. The specimens were analyzed for blood citrate, calcium, pH, and total protein. The calculations of ionizable calcium were determined by a process of successive approximations using the nomograms of MacLean and Hastings.[7]

Analysis of data

Serial specimens obtained at 5 minute intervals during normothermia and hypothermia were analyzed for blood citrate. Consistently higher levels were observed in hypothermic dogs when comparison was made with the levels in normothermic controls. A graph demonstrating this reduction in citrate metabolism during hypothermia is shown in Fig. 1.

Electrocardiographic changes induced by hypothermia (29°C. rectal temperature) were characteristic Osborn waves, ST-T change, and prolonged atrioventricular and intraventricular conduction time which have been previously described.[1-4] The infusion of citrate tended to produce (1) more Q-T *prolongation than did hypothermia* alone, and (2) an electrical alternans of the T wave. This latter change was not detected by us when hypothermia was used alone. The mechanism of this abnormality is not apparent, although it is probably associated with a change in myocardial metabolism.

The alternating T change was seen one time during infusion of citrate into a normothermic animal. This suggests that this may be an electrocardiographic change associated with administration of citrate exclusive of hypothermia.

Three types of alternating T changes were observed and are shown in Figs. 2 and 3.

The following is a useful qualitative descriptive classification of the T wave changes observed. *Type I*: Alternating T wave consisting of a slight lowering of the T wave in every other complex (marked with Roman numeral I over arrow at 25 minutes in Fig. 3*A*). *Type II*: Alternating T wave showing every other T wave more deeply negative (marked in Fig. 2 with Roman numeral II). This is the most frequently observed variety. *Type III*: Alternation of the T wave with one complex exhibiting a flat or biphasic T wave and the second complex showing a negative wave (marked Roman numeral III in Fig. 2).

It was felt that a more comprehensive description of the T alternans would include many subtypes which might be confused with changes ordinarily seen in hypothermia alone.

A summary of the data obtained on 4 representative animals is presented in Table I and Figs. 3 and 4. There would appear to be little correlation between the appearance of T alternation and any change observed except the level of citrate in the blood. T alternation appeared with a fair degree of consistency at a level of approximately 70 mg. per cent of citrate in the blood of the hypothermic animals. Dog No. 8 (Table I and Figs. 3 and 4) failed to exhibit any T

An ... hyd... ...ed ... wa first d... ed during hypothermia by J. J. Osborn ... d ... wn in Fig. 2.

alternation however in spite of levels of 83 2 mg /100 c c Dog No 7 (Table I and Figs 3 and 4) exhibited marked T wave changes while hypothermic and slight T wave changes under normothermic conditions

A fall in mean blood pressure was observed during infusion of ACD into hypothermic animals and often when T wave alternans appeared an alternating pressure curve was observed as well (Fig 4) Very close inspection will reveal a slight QRS alternans at times however this is not noticeable in most of the observations Dog No 8 exhibited fairly noticeable hypothermic changes in the electrocardiogram but failed to exhibit T alternans attributable to the administration of citrate Dog No 10 revealed marked T alternation during hypothermia None of the other 8 animals exhibited any T alternation during

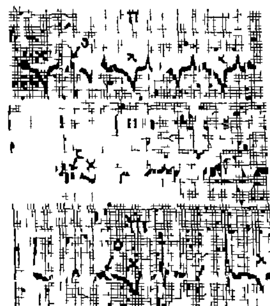


Fig 2 Electrocardiograms demonstrating three examples of T alternation observed during hypothermia and infusion of citrate All traces demonstrat early dia tolic O born es (marked *O*) usually seen in hypothermia as ell as T alternans Complexes howing the more deepl negativ lte nat T es are marked \ Type-II and Type-III changes described in text are marked Changes of this magnitude were observed with level of blood citrate of 50 mg per cent and abov usually 0 mg per cent and abov These examples are all selected from nimal fter 25 minutes of infusion of ACD th les l of blood citrate of 90 mg per cent or more

normothermia During hypothermia all exhibited T alternation of the types shown in Figs 2 3 and 4

Other experiments in this laboratory have indicated that no consistent alternation in the serum potassium is observed during ACD infusion of this type and this determination was not performed in the present study

Changes in blood pH are known to produce marked changes in the electrocardiogram and some of the observed effects may reflect subtle changes in pH attendant on the administration of ACD It is noted however that little correlation exists between changes in the blood pH and the electrocardiographic changes observed during the experiments (Table I) The blood pH of the dogs was generally higher when they were hypothermic than when they were normothermic During infusion of ACD however the pH was not observed to be consistently higher or lower than the control determination We feel that the differences in pH may be explained by differences in ventilation since the ACD solution was buffered to normal serum levels

Animals rendered hypothermic exhibit a general slowing of body metabolism This results in a similar reduction in the metabolism of most drugs administered during the hypothermic state as has been demonstrated for citrate (Fig 1) Hypothermia is similarly responsible for slow cardiac rates and hypotension

T alternation was usually accompanied by a prolongation of the Q T interval (see Table I) and this finding was demonstrated in all of the animals in this study except 2 Fig 5 is a graph which illustrates the relationship of the Q T interval to the level of citrate in the 4 representative experiments described previously Note that an increase in the Q T interval usually accompanies a rise in the level of citrate in the blood and the averages of increases in Q T interval during infusion when plotted against the level of citrate for both hypothermic and normothermic animals produced curves that are significant in normothermic animals to $p = 0.025$ and in hypothermic animals to $p = 0.010$ (linear regression) The most pronounced effect on the Q T interv is observed in the hypothermic group

Table I

		Dog No. 7						Dog No. 8					
Time (min.)		Control 0	5	10	15	20	25	Control 0	5	10	15	0	5
P-R (sec.)	N	0.08	0.09	0.08	0.08	0.075	0.08	0.12	0.11	0.09	0.10	0.09	0.10
	H	0.13	0.12	0.1	0.12	0.12	0.16	0.12	0.13	0.12	0.12	0.12	0.13
QRS (sec.)	N	0.05	0.05	0.05	0.05	0.05	0.05	0.06	0.05	0.05	0.05	0.05	0.05
	H	0.08	0.07	0.08	0.07	0.06	0.06	0.07	0.08	0.07	0.07	0.07	0.07
Q-T (sec.)	N	0.26	0.26	0.24	0.24	0.25	0.7	0.28	0.24	0.25	0.26	0. 5	0.24
	H	0.43	0.44	0.54	0.56	0.54	0.60	0.30	0.37	0.37	0.3	0.13	0.33
Rate per min.	N	150	154	165	160	162	155	170	140	140	150	150	155
	H	96	94	90	92	96	73	144	145	145	140	140	142
Mean pressure (mm. Hg)	N	126	126	115	170	115	120	120	100	50	45	25	55
	H	65	50	40	35	20	15	135	125	115	115	110	115
Citrate (mg. %)	N	4.0	37.0	49.6	57.6	0.4	90.4	2.8	35.6	32.0	56.0	67.2	72.0
	H	3.2	49.2	60.0	81.6	148.8	100.8	1.2	78.0	36.0	61.8	93	93.2
Calcium (mg. %)	N	9.8	—	9.5	—	10.1	—	7.8		10.8		7.9	—
	H	10.8	—	10.2	—	10.5	—	11.5		10.1	—	9.9	—
Ionized calcium (mM/L.)	N	1.00	0.2	0.48	0.40	0.38	0.34	0.49	0.32	0.18	0.14	0.17	0.14
	H	1.00	0.40	0.4	0.38	—	—	1.45	1.05	0.69	0.58	0.42	0.42
pH	N	7.5	—	7.55	—	7.55	—	7.5	—	5	—	7.5	—
	H	7.7	—	7.6	—	7.65	—	7.5	—	7.55	—	7.55	—
Total protein (Gm. %)	N	6.8	—	7.0	—	7.0	—	4.9	—	4.4	—	4.5	—
	H	8.3	—	7.3	—	6.6	—	5.5	—	5.4	—	5.0	—

Pressure curve damped.
N, Normal; H, Hyper[illegible]

Table 1—Cont'd

Time (min)		Dog No 10: Cont 0	5	10	15	20	25	Dog No 12: Control 0	5	10	15	20	25
P-R (sec)	N	0.10	0.08	0.08	0.08	0.09	0.10	0.08	0.09	0.08	0.09	0.09	0.05
	H	0.14	0.12	0.12	0.12	0.14	0.16	0.12	0.13	0.15	0.14	0.14	0.14
QRS (sec)	N	0.01	0.04	0.04	0.04	0.04	0.04	0.01	0.04	0.04	0.04	0.04	0.01
	H	0.07	0.06	0.07	0.06	0.08	0.08	0.06	0.06	0.07	0.08	0.08	0.06
Q-T (sec)	N	0.17	0.22	0.1	0.21	0.20	0.22	0.20	0	0.20	0.20	0.22	0.21
	H	0.33	0.32	0.36	0.40	0.46	0.43	0.35	—	0.38	0.39	0.44	0.46
Rate per min	N	130	160	162	160	155	150	150	155	160	160	160	170
	H	106	109	100	90	90	97	170	150	115	110	103	100
Mean pressure (mm Hg)	N	145	145	120	170	110	110	120	100	150	190	155	130
	H	110	105	100	75	0	60	120	120	113	110	85	90
Citrate (mg %)	N	1.6	36.0	39.0	49.6	64.0	60.0	3.6	24.0	37.6	48.8	59.2	61.0
	H	2.4	44.4	63.2	90.0	10 0	121.6	6.4	33.6	54.0	76.0	86.4	116.0
Calcium (mg %)	N	11.6	—	11.4	—	10.0	—	12.4	—	12.2	—	11.1	—
	H	11.2	—	10.7		10.8	—	11.4	—	11.0	—	11.2	—
Ionized calcium (mM/L)	N	1.4	0.84	0.80	0.70	0.30	0.30	—		—		—	—
	H	1.41	0.99	0.61	0.50	0.52	0.38	1.41	0.99	0.61	0.50	0.57	0.38
pH	N	7.45	—	7.5	—	7.3	—	7.4	—	7.4	—	7.4	—
	H	7.6		7.6	—	7.6	—			—	—	—	—
Total protein (Gm %)	N	6.1		5.5	—	5.5	—	6.1	—	5.8	—	5.5	—
	H	5.5		4.9	—	4.6		6	—	6.6	—	6.0	—

[illegible]

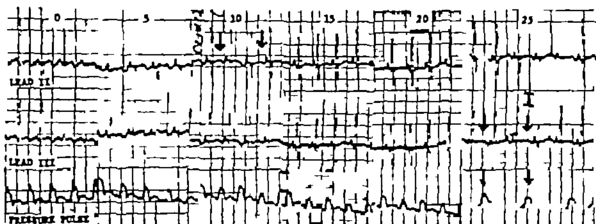


Fig. 4. Representative portions of [illegible] hypothermic dogs. ECG Lead II, III, and simultaneous pressure pulse. Pulse waves [illegible] for contour only; for exact determination of pressure see Table I. Time in minutes is shown at the top of each figure. A, Dog No. [illegible] demonstrates T alternans while normothermic during infusion of citrate. The best ECG sample of alternans is seen at 10 min.; pulse contour alternans appears at 2 min. These changes are designated by arrows. B, Dog No. 8. Note lowering of T wave in ECG tracings subsequent to the [illegible]. [illegible] contour badly damped. C, Dog No. 10. Little change in the ECG is seen during entire experiment. The contour tends to change with fall in mean blood pressure. D, Dog No. 12. Very high T wave changes (alternans) are observed. Pressure pulse contour is damped at 5 min.

Q-T measurements were not corrected for rate, because the usual formulas for correction of the Q-T interval are not particularly applicable at the fast and slow rates observed in these experiments. The effect of hypothermia alone in the production of the slow rate might account for the control observation of the prolonged Q-T interval; however, since the body temperature remained relatively constant, further prolongation which occurred during the infusion of ACD may be taken as an effect of the infusion.

The effect of the infusion of ACD on serum calcium was of interest, since citrate is known to depress the plasma ionized calcium. Unfortunately, no generally satisfactory method is available for the determination of ionized calcium, and one must rely upon the calculated figures shown in Table I. Generally, values of ionized calcium are lower during hypothermia and infusion of ACD; however, Dog No. 8 demonstrates that this finding was not consistent. Infusion of ACD did, however, depress the ionized calcium to values below control level in every instance, including Dog No. 8, in which T alternation was not detected. We conclude that the levels of ionized calcium or of serum calcium do not correlate well with the appearance of T alternation seen in our experiments.

Discussion

The electrocardiographic demonstration of T alternans was of greatest interest to us, since we had not seen such a striking T change without the more common type of electrical alternans involving the QRS complex. Close inspection of the tracings presented here will reveal slight degrees of QRS alternans; however, this change is not so readily apparent as the changing T wave. As with the QRS type of alternans, the pulse wave occasionally exhibited this alternating phenomenon (Fig. 4). T alternans has apparently been produced to a lesser degree through the administration of triiodothyronine. The possibility of alteration of the transmembrane potential in some fashion which renders the cell (or cells) more or less permeable to certain ions has been suggested as a hypothesis to explain this phenomenon; however, the metabolites and the exact mechanisms involved are obscure.

There is a paucity of information in regard to the effect of various drugs administered under hypothermic conditions in animals and in man. Hypothermia does cause an over-all reduction in bodily function at almost every level, and administered substances tend to accumulate more rapidly because of ineffective metabolism and/or excretion. Fisher and associates have



Fig 3 B

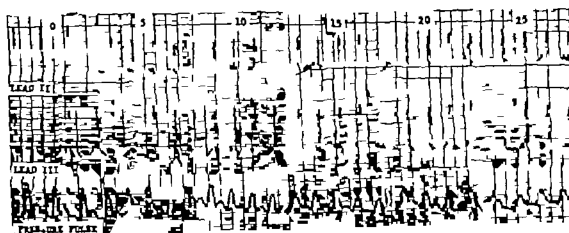


Fig 3 C

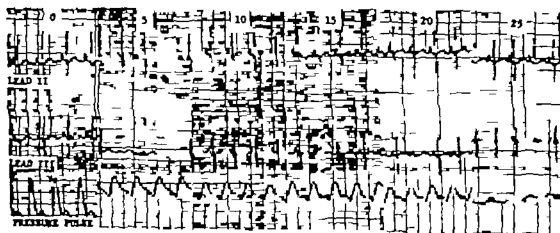
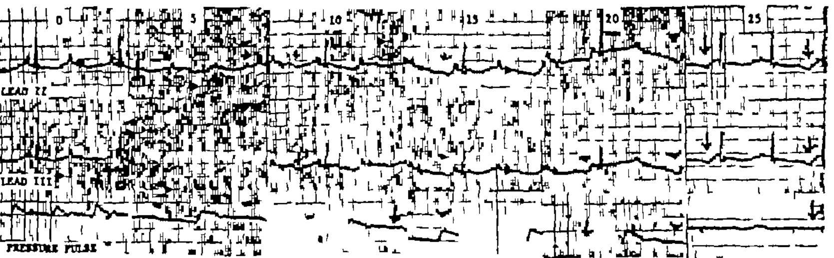


Fig 3 D



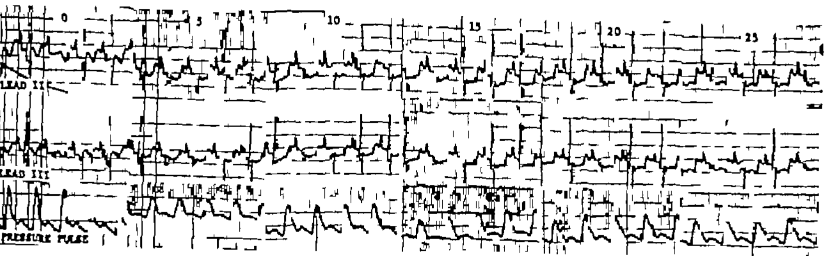


Fig. [illegible] experiment [illegible] hypothermic [illegible] ECG [illegible] II and III and simultaneous pressure pulse [illegible] only [illegible] determinations of pressure see Table I. Time in minutes is shown at top of each figure. ECG and pulse pressure changes [illegible] arrow [illegible] Control ECG shows type I hypothermic change [illegible] Lead III at 10 min. [illegible] alternans [illegible] ECG recorded during [illegible] and pressure pulse alternation. Type II changes throughout [illegible] Not [illegible] the type [illegible] seen [illegible] not [illegible] during this experiment [illegible] Although additional [illegible] occurred during [illegible] alternans of



Fig. 4—Cont'd. *C*, Dog No. 10. Alternans apparent at 10 min. Pulse contour alternation detected at 20 min. Type II changes throughout. *D*, Dog No. 12. *Marked* ST-T changes throughout. Type I alternans began at 5 min. Successive tracings reveal Type II changes from 10 through 25 min. Electrical alternans seen only at 25 min.

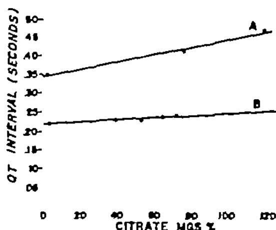


Fig. 5. The effect of the infusion of citrate on the Q-T interval in normothermic and hypothermic dogs. Curve A represents an average of the Q-T intervals and levels of citrate in 4 hypothermic dogs annotated in Table I and Figs. 3 and 4. Curve *B* represents the same calculations in these dogs under normothermic conditions. Note the initial higher level and more profound effect of citrate on the Q-T interval in the hypothermic animal. These curves are statistically significant by linear regression. The Q-T interval is not corrected for rate because the comparison of the tachycardias and bradycardias associated with barbiturate anesthesia and hypothermia, respectively, makes the usual formulas inapplicable. The feature that is of most interest, however, is that the infusion of ACD causes proportionately more prolongation under hypothermic than normothermic conditions.

noted the depressant effect of hypothermia on the functioning of the liver. This undoubtedly plays a large part in the apparent decrease in tolerance to, or increased effect of, substances detoxified or modified by the liver which were administered during the hypothermic state. Hubbard and associates[11] report a case of severe citric acid intoxication occurring during an infundibular resection because of a tetralogy of Fallot. Their patient developed hypotension and electrocardiographic changes after receiving 750 c.c. of citrated bank blood over a 20 minute period. These changes were apparently corrected through administration of calcium. Inspection of their illustration reveals Type I T alternans during administration of the citrated blood.

It is also of interest to speculate that the changes of T alternation observed may represent changes in the U wave rather than intrinsic changes in the T wave. The appearance of early T wave changes as well as late changes would seem to make this less likely but still a possibility.

Bobin[11] has stated that a peculiar early diastolic wave (Osborn wave) is related to the appearance of ventricular fibrillation during hypothermia. All of the hypothermic tracings reproduced here demonstrate the Osborn wave and we have not been impressed with its value in predicting the onset of ventricular fibrillation. We are certain, however, that this wave is present in most of the animals rendered sufficiently hypothermic for the induction of ventricular fibrillation. Our electrocardiographic experience with hypothermia leads us to conclude that there are no characteristic changes which precede ventricular fibrillation and that the Osborn or early diastolic wave is not an ominous sign.

One of the authors (J. I. D.) had the opportunity of monitoring the electrocardiogram on a patient under hypothermia for operation on an aneurysm of the circle of Willis. Massive hemorrhage led to the rapid (5 minute) infusion of 1,000 ml. of citrated bank blood. Type II alternans of the T wave was induced. The patient subsequently recovered without sequelae.

Summary

Data have been presented which demonstrate changes in the electrocardiogram of normothermic and hypothermic dogs during the intravenous infusion of buffered ACD solution.

The most striking change was an electrical alternans of the T wave which occurred in varying degrees but which was present in all animals except one under hypothermia. Osborn waves and P-R, QRS, and Q-T prolongation were also demonstrated. Normothermic animals demonstrated slight Q-T prolongation and T wave lowering, rarely a modest form of T alternans.

The possibility exists that the electrocardiographic T alternans was a result of a reduction in the level of the ionized serum calcium; however, the data presented neither support nor disprove this hypothesis.

The T alternans described was noted to occur in a human patient under hypothermia and rapid transfusion. It is not an ominous sign and was not associated with increased mortality during animal experiments or in the human subject mentioned above.

The authors gratefully acknowledge the technical assistance of Marilyn H. Lile, M.T., and wish to express thanks to Mr. Fred Jungklaus for the photographic reproduction of graphs and electrocardiograms and to Dr. S. William Ross for assistance in calculation of ionized calcium.

REFERENCES

1. Osborn, J. J.: Experimental hypothermia: respiratory and blood pH changes in relation to cardiac function, Am. J. Physiol. 175: 389, 1953.
2. Hicks, C. E., McCord, M. C., and Blount, S. G., Jr.: Electrocardiographic changes during hypothermia and circulatory occlusion, Circulation 13: 1, 1956.
3. Emslie-Smith, D., Sladden, G. E., and Stirling, G. R.: The significance of changes in the electrocardiogram in hypothermia, Brit. Heart J. 21: 343, 1959.
4. Argent, D. E.: Citrate intoxication following rapid massive blood transfusion, Brit. J. Anaesth. 29: 136, 1957.
5. Ludbrook, J., and Wynn, V.: Citrate intoxication: clinical and experimental study, Brit. M. J. 2: 523, 1958.
6. Hastings, A. B., MacLean, F. C., Eichelberger, L., Hall, J. L., and DaCosta, E.: The ionization of calcium, magnesium and strontium citrates, J. Biol. Chem. 107: 351, 1934.
7. MacLean, F. C., and Hastings, A. B.: The state of calcium in the fluids of the body, J. Biol. Chem. 108: 285, 1935.
8. Hara, M., Doherty, J. E., and Williams, D.: Citric acid metabolism in the hypothermic dog. (To be published.)
9. Kleinfeld, M.: Experimental modification of the transmembranal potential relation to myocardial mechanics: alternation of the action potential. *In* Advances in electrocardiography, edited by C. E. Kossmann, New York, 1958, Grune & Stratton, Inc.
10. Fisher, B., Fedor, E. J., Lee, S. H., Weitzel, W. K., Selker, R., and Russ, C.: Some physiologic effects of short- and long-term hypothermia upon the liver, Surgery 40: 862, 1956.
11. Hubbard, T. F., Neis, D. D., and Barmore, J. L.: Severe citrate intoxication during cardiovascular surgery, J. A. M. A. 162: 1534, 1956.
12. Bobb, A.: Abnormal electrocardiographic pattern and its relation to ventricular fibrillation (observations during clinical and experimental hypothermia), Am. Heart J. 57: 53, 1959.

A prong-catheter for inducing vascular distention in the intact animal

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In cardiovascular research it is sometimes desired to study the effects in the intact animal of localized vascular distention. The preferred method at present consists of passing a Dotter-Lukas (balloon) catheter to the experimental site and then to inflate the balloon. The difficulty arises, however, in that the inflated balloon obstructs the flow of blood, making interpretation of results obtained by this method disputable.

The present communication describes a new instrument for distending blood vessels without obstructing flow.

Methods and results

The device consists of 4 pieces of staggered lengths (circa 1 3/4 inches) of .022 inch spring steel wire soldered onto a .045 inch spring steel wire which runs the entire length of a 50 cm., size 10F, radiopaque Cournand catheter (Fig. 1). These 4 wires are bent outward so as to form a spreader approximately 1[illegible] inches in diameter, which retracts into a tube 2[illegible] inches long made from [illegible] inch brass tapered on both ends externally and threaded onto the outer diameter of the catheter. The tube is counterdrilled [illegible]

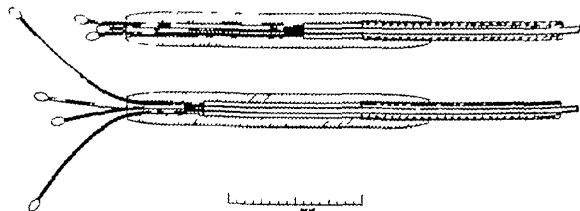


Fig. 1. Engineering diagram of the prong catheter. *Above:* Spreader retracted. *Below:* Spreader expanded.

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Fig. 2. X ray photograph of the prong catheter expanded in the inferior vena cava near its entrance into the right auricle. The other catheters have been positioned in the chambers of the heart for the recording of pressure.

inch on its proximal end to accommodate a 6/32 inch tap so that it cuts its own thread when screwed onto the catheter but not deeply enough to damage it. The tips of the wires have small knobs of solder to prevent them from puncturing the walls of the blood vessel when expanded. The proximal end of the long wire has a handle for grasping.

The catheter is ready for insertion into a vessel when the wires are retracted into the tube. By pushing forward on the handle the prongs are released distally and the vessel is distended (Fig. 2).

Conclusions

The above described instrument shows promise of very practical usefulness in cardiovascular research since it is possible to position the catheter in any desired accessible area of the vascular tree, permitting local mechanical vascular distention without the inconvenience of blocking the flow of blood. We have found this device useful in studies involving the afferent initiation of the Bainbridge reflex. These will be reported in a separate publication.

Summary

A new prong catheter is described that permits vascular distention in the intact animal as a tool for studying certain cardiovascular reflexes.

REFERENCES

1. Klossman, F. W., Van Citters, R. L. and Rushmer, R. F. Cardiovascular effects of distortion of stretch receptors in the cardiac wall. Fed. Proc. 19: 92, 1960.
2. Cross, C. E., Salisbury, P. E. and Rieben, P. A. Reflex effects of left ventricular distention. Fed. Proc. 19: 104, 1960.
3. Ballin, J. R. and Katz, L. N. Observations on the localization of the receptor area of the Bainbridge reflex. Am. J. Physiol. 135: 202, 1941.

The systemic and coronary hemodynamic effects of 1-(2 methoxyphenol)-4-(3 methoxypropyl)-piperazine phosphate

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An antihypertensive drug which has recently been made available is 1-(2 methoxyphenol)-4-(3 methoxypropyl)-piperazine phosphate (Ansax), also known as Abbott HT 1479. It has been shown to lower the blood pressure of both normotensive and hypertensive experimental animals and to produce slight changes in coronary blood flow as measured by Moravitz cannula or Langendorff perfusion. Since the agent has some clinical promise, a pharmacologic study in experimental animals was undertaken in order to elucidate its hemodynamic effects in more detail.

Material and methods

The study was done in 10 mongrel dogs which varied in weight between 18 and 30 kilograms. The animals were anesthetized by 3 mg. per kilogram of morphine sulfate given subcutaneously and followed in 1 hour by intravenous administration of 0.25 ml. per kilogram of a 50:50 mixture of Dial urethane and veterinary pentobarbital. After anesthesia was secured, cardiac catheters were maneuvered fluoroscopically into the pulmonary artery, the right atrium, and the coronary sinus, and Cournand needles were placed percutaneously in each femoral artery.

Cardiac output was determined by the direct Fick principle, and expired air was collected via a cuffed endotracheal tube and a Tissot spirometer. Gas analyses were done by the Van Slyke–Neill method on blood specimens and by the Scholander method on expired air. Coronary flow was determined by the nitrous-oxide saturation method. The nitrous oxide analyses were made by the method of Orcutt and Waters. The pH was determined on whole blood by means of the Cambridge model R pH meter. In 9 animals during the determination of cardiac output by the Fick principle and again during the measurement of coronary blood flow, cardiac output was also

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Dial urethane furnished by the courtesy of CIBA Pharmaceutical Products, Inc., Summit, N. J., contains Dial 100 mg./ml., monoethylurea 400 mg./ml., and urethane 400 mg./ml. Veterinary Nembutal contains 60 mg./ml. of sodium pentobarbital.

determined by the Hamilton indicator dilution method using the Gilford model 103 IR densitometer and indocyanine green as the indicator substance. The indicator was injected into the pulmonary artery and sampling was done from the femoral artery with a constant withdrawal pump set to withdraw at a rate of 25 c.c. per minute. Each curve was calibrated by using known concentrations of indicator in whole arterial blood from the dog under study. The indicator dilution curves, pressure curves, and electrocardiogram was recorded by the Gilson direct writing macropolygraph. Statham strain gauges were used for all pressures and the mean pressures were determined by electrical integration. Standard formulas were used for all calculations.

After control determinations the animals were given either 0.5 or 1 mg. per kilogram of Anm rapidly into the pulmonary artery or coronary sinus (one half of the animals received each dose) approximately 20 minutes subsequent to the administration of Anm, the second determination of the cardiac output was made and was followed by determination of coronary flow.

Results

Results of the study are summarized in Table I. It will be seen that there was a significant increase in cardiac rate (+54.0 per cent, $p < 0.01$) accompanied by a significant decrease in mean blood pressure in the systemic and pulmonary arteries. Right atrial pressure decreased in 9 out of 10 animals. The minute volume of respiration increased significantly (+37 per cent, $p < 0.05$) and there were slight but significant increases in both the consumption of oxygen and the elimination of carbon dioxide. The respiratory quotient also increased slightly. On the other hand, the arterial and mixed venous oxygen contents as well as the arteriovenous oxygen difference remained unchanged. Apparently associated with the increased ventilation

Table I. Hemodynamic effects of HT 1479

Parameter	Control ± S.E.M.	Drug ± S.E.M.	% Change	p value <
Cardiac rate	87 ± 7	134 ± 13	+54.0	0.01
Mean systemic arterial blood pressure (mm. Hg)	112 ± 4	93 ± 3	−17.0	0.01
Mean pulmonary arterial blood pressure (mm. Hg)	15 ± 2	13 ± 2	−13.3	0.05
Mean right atrial blood pressure (mm. Hg)	3.0 ± 0.3	1.5 ± 0.7	−50.0	0.1
Volume respiration (L./min.)	2.7 ± 0.2	3.7 ± 0.5	+37.0	0.05
Oxygen consumption (ml./min.)	107 ± 7	115 ± 8	+ 5	0.05
Carbon dioxide elimination (ml./min.)	87 ± 6	98 ± 7	+12.6	0.01
Body respiratory quotient	0.80 ± 0.01	0.86 ± 0.0	+ 7.5	0.05
Arteriovenous oxygen difference (ml./100 ml. blood)	4.7 ± 0.4	4.6 ± 0.4	− 2.1	0.8
Mixed venous carbon dioxide content (ml./100 ml. blood)	50.6 ± 1.0	47.5 ± 1.1	− 6.1	0.001
Venoarterial carbon dioxide difference (ml./100 ml. blood)	3.5 ± 0.1	3.8 ± 0.4	+ 8.6	0.6
Coronary sinus oxygen content (ml./100 ml. blood)	4.3 ± 0.6	3.[illegible] ± 0.4	−25.6	0.05
Arterial coronary sinus oxygen difference (ml./100 ml. blood)	11.7 ± 0.5	13.2 ± 0.6	+12.8	0.05
Coronary sinus carbon dioxide content (ml./100 ml. blood)	55.3 ± 1.1	53.0 ± 1.3	− 4.2	0.05
Arterial coronary sinus carbon dioxide difference (ml./100 ml. blood)	10.2 ± 0.5	11.4 ± 0.5	+11.8	0.01
Cardiac respiratory quotient	0.88 ± 0.03	0.87 ± 0.03	− 1.1	0.8
Arterial hematocrit reading	43 ± 1	43 ± 2	—	—
Arterial pH	7.24 ± 0.01	7.[illegible]5 ± 0.02	+ 0.1	0.2
Coronary sinus pH	7.21 ± 0.0	7.22 ± 0.02	+ 0.1	0.3
Cardiac output (L./min.)	2.5 ± 0.3	2.7 ± 0.2	+ 8.0	0.6
Stroke volume (ml.)	30 ± 4	21 ± 3	−30.0	0.01
Total peripheral resistance (units)	4,038 ± 498	2,912 ± 253	−27.9	0.02
Total pulmonary resistance (units)	515 ± 67	414 ± 85	−19.6	0.1
Left ventricular work (Kg. M./min.)	3.8 ± 0.5	3.4 ± 0.4	−10.5	0.2
Right ventricular work (Kg. M./min.)	0.5 ± 0.1	0.5 ± 0.1	—	—
Coronary blood flow (ml./100 Gm./min.)	87 ± 6	83 ± 4	− 4.6	0.6
Cardiac oxygen usage (ml./100 Gm./min.)	10.0 ± 0.5	10.9 ± 0.8	+ 9.0	0.4
Coronary vascular resistance (units)	1.33 ± 0.09	1.14 ± 0.07	−14.3	0.2
Index of efficiency	0.38 ± 0.04	0.37 ± 0.03	−15.8	0.1

there was a decrease in the mixed venous and arterial carbon-dioxide content with an unchanged mixed venous arterial carbon dioxide difference The oxygen content of coronary sinus blood decreased significantly (−25 6 per cent $p < 0.05$) with a significant increase in the arterial coronary sinus oxygen difference (+12 8 per cent $p < 0.05$) Although the carbon-dioxide content of coronary sinus blood decreased (−4 2 per cent $p < 0.05$) it decreased less than did the arterial carbon-dioxide content with the coronary sinus–arterial carbon dioxide difference increasing significantly (+11 8 per cent $p < 0.01$) The cardiac respiratory quotient was unchanged Neither the arterial hemoglobin nor the hematocrit changed significantly in the experimental as compared to the control observations When the control observations were compared with the experimental observations there were no significant changes in pH in the femoral arterial or in the coronary sinus blood

Cardiac outputs as determined by the indicator dilution method averaged 0 3 L per minute less than those determined by the Fick principle This difference was statistically significant ($p < 0.01$) Hence those outputs measured by the Fick principle are used in the table and in the calculations Comparison of the cardiac outputs determined by the Hamilton method first during the determination of the cardiac output by the Fick principle and again during the determination of coronary blood flow showed no significant difference between these determinations There was an average difference between these two determinations of only 0 1 L per minute indicating a fairly steady state throughout the procedure

There was no difference in cardiac output in the control as compared to the experimental period whether the figures derived from the Fick or those from the Hamilton methods are compared Central blood volume as calculated from the Hamilton indicator-dilution curves indicate a slight but insignificant reduction after the administration of Ansv Total peripheral resistance was reduced (−27 9 per cent $p < 0.02$) and left ventricular work decreased slightly (10 5 per cent) but not significantly There were no significant differences in coronary hemodynamics although coronary blood flow tended to decrease (−4 6 per cent $p < 0.6$) as did coronary vascular resistance whereas myocardial oxygen usage per 100 grams tended to increase

Discussion

The search for desirable antihypertensive drugs continues with one of the goals an agent which will reduce peripheral vascular resistance so as to permit the hypertensive subject to maintain normal blood flow at a lower systemic arterial pressure Hydralazine is such an agent since it produces hypotension accompanied by increased cardiac output and increased cerebral renal and coronary blood flow[4] The ganglion blocking group of drugs and chlorothiazide insofar as information is available have produced hypotension chiefly through decreasing cardiac output It is of considerable interest then for a hypotensive agent to reduce blood pressure without decreasing cardiac output as Ansv has done in this study These results are of greater interest since cardiac output was maintained in spite of reduced venous filling pressure in 9 of the 10 animals This may indicate that the administration of Ansv is associated with a more favorable Starling performance curve although in the absence of data concerning end-diastolic pressures in the two ventricles this cannot be determined as defined by Sarnoff[11] When the calculated external efficiency of the heart is compared before and after the administration of Ansv the amount of work done per unit of oxygen consumed is actually slightly less (−15 8 per cent $p < 0.1$) This may well be related to the cardiac acceleration which accompanied the administration of the drug in these animals since cardiac acceleration is known to affect efficiency adversely At the same time it should be pointed out that coronary blood flow per unit of work done is actually increased after administration of the drug

Clinical studies reported recently have indicated that Ansv produces considerable hypotension when administered either orally or intravenously to hypertensive subjects[12] It is of great interest that in these subjects *renal vascular resistance fell during the early* and late hypotensive phases but

rose during the trough of the response Renal blood flow decreased as blood pressure reached its trough but was quite well maintained in the milder early and late hypotensive phases Unfortunately the clinical response has been transient and the side effects have been excessive when Ansu was used as the sole agent in therapy [13] Whether the drug or its modifications will eventually be useful is not known however its hemodynamic actions as reported[13] and as seen in the present study are of sufficient interest to merit consideration

Conclusions

1 The systemic and coronary hemodynamic effects of 1 (2 methoxyphenol)-4 (3 methoxypropyl) piperazine phosphate (Ansu HT 1479) have been studied by intravenous administration of the drug to a series of 10 anesthetized mongrel dogs

2 Its administration was associated with a statistically significant decrease in peripheral and pulmonary arterial blood pressure and a decrease in right atrial pressure in 9 of the 10 animals

3 Subsequent to its administration cardiac output and coronary blood flow were maintained whereas total peripheral resistance was reduced and coronary vascular resistance tended to be reduced

4 After administration of the drug there was a considerable increase in cardiac rate and a slight but insignificant decrease in cardiac efficiency

REFERENCES

1 Murphy B B Roth L W and Richard R K Pharmacologic studies of new antihypertensive compound (o-methoxyphenyl) (3 methoxypropyl) piperazine phosphate (HT 14 9) Proc Soc Exper Biol & Med 101 174 1959

2 Rowe G G Huston J H Maxwell G M Crosley A P J and Crumpton C W Hemodynamic effects of 1 hydrazinophthalazine in patients with arterial hypertension J Clin Invest 31 113 1955

3 Crumpton C W Rowe G G Crosley A P J Maxwell G M and Huston J H Cardiovascular cerebral and renal hemodynamics and metabolic adjustments to 1 hydrazinophthalazine in essential hypertension J Lab & Clin Med 42 797 1953

4 Crosley A P J Rowe G G and Crumpton C W The hemodynamic and metabolic response of the human hypertensive kidney to standard dose of 1 hydrazinophthalazine (hydralazine) J Lab & Clin Med 44 104 1954

5 Rowe G G Huston J H Maxwell G M Weinstein A B Tuchman H and Crumpton C W The effects of 1 hydrazinophthalazine upon coronary hemodynamics and myocardial oxygen metabolism in essential hypertension J Clin Invest 34 696 1955

6 Crumpton C W Rowe G G O Brien G and Murphy Q R The effect of hexamethonium bromide upon coronary flow cardiac work and cardiac efficiency normotensive and renal hypertensive dogs Circulation Res 2 79 1954

7 Crosley A P J Brown J F Tuchman H Crumpton C W Huston J H and Rowe G G The acute hemodynamic and metabolic response of hypertensive patients to pentolinium tartrate Circulation 13 584 1956

8 Rowe G G Castillo C A Maxwell G M White D H J Freeman D J and Crumpton C W The effect of mecamylamine on coronary flow cardiac work and cardiac efficiency in normotensive dogs J Lab & Clin Med 52 883 1958

9 Crosley A P J Castillo C Freeman D J White D H J and Rowe G G The acute effects of carbonic anhydrase inhibitors on systemic hemodynamics J Clin Invest 37 887 1958

10 Dustan H P Cummings G R Corcoran A C and Page I H A mechanism of chlorothiazide-enhanced effectiveness of antihypertensive ganglioplegic drugs Circulation 19 360 1959

11 Sarnoff S J Myocardial contractility as described by ventricular function curves observations on Starling s law of the heart Physiol Rev 35 107 1955

12 Maxwell G M Castillo C A White D H Jr Crumpton C W and Rowe G G Induced tachycardia its effect upon the coronary hemodynamics myocardial metabolism and cardiac efficiency of the intact dog J Clin Invest 37 1413 1958

13 Rosenfeld J B Brest A N Duarte C and Moyer J H Pharmacological effects of 1 (2 methoxyphenol)-4 (3 methoxypropyl) piperazine phosphate (HT 1479) on hypertensive patients Antibiotic Med 171 1960

A study of the normal Frank vectorcardiogram

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The Frank system of spatial vectorcardiography has been proposed as an electrically orthogonal method and has an advantage in its ease of application. Its theoretical accuracy and the results of comparison with other corrected systems have provided a reasonable basis for its further investigation and clinical use. Despite this, there are few published guides for the differentiation of normal and abnormal vectorcardiograms obtained with this method. Some reports have presented experience with scalar lead recorded with the Frank system. Limited descriptions of the normal range are available in terms of QRS-Ê and T-Ê loop axes. These investigations included application of the system to patients with heart disease. Comparisons of the Frank system with the electrocardiogram and other vectorcardiographic reference frames are available, but without detailed description of normal findings. Spatial vectorcardiographic recording of the QRS-Ê loop with Frank leads was described by Seiden, but information concerning the T-Ê loop and vector magnitudes was not given.

The purpose of this study was to obtain direct spatial vectorcardiograms (VCGs) with the Frank system in a group of subjects who were free of cardiovascular disease. The results are to serve as preliminary normal standards for use in comparison with findings in groups of subjects with pathologic conditions. It was of interest to compare the findings with those published for the SVEC III and lead field methods.

Material and Methods

Seventy-two subjects were studied. Fifty-three were faculty members, resident physicians, interns, or medical students at the University of Oregon Medical School Hospitals and Clinics. The remainder was constituted of inpatients in the University Hospital. There were no findings or history of cardiac disease in any of the people included in the study. Routine 13 lead electrocardiograms which were normal were obtained just before or after the vectorcardiographic examination in all of the subjects. Because of the source of the subjects, only 4 women were included in the series. The age distribution of the group is shown in Table I.

The placement of electrodes and the lead resistance network employed were as proposed by Frank. The fifth intercostal space at the sternal border was used in all cases as the level for the chest leads. Frank's point C, located 45 degrees between the anatomic axes of points A and E, was found by inspection. The examination was performed with the subject seated comfortably. The three planar projections of the VCG were photographed from the oscilloscope screen with a 35 millimeter camera. Exposures were made at the end of an ordinary expiration with the breath held briefly. Sagittal projections were viewed from the left side as previously recommended.[11] The film was projected in an enlarging viewbox with a screen 11 by 11 inches, and tracings were made on paper for definitive study. A 1 millivolt calibra-

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tion signal in the horizontal and vertical axes was also photographed to serve as a reference standard for the enlargements The magnification provided traced records in which 3 5 inches (9 0 cm) equalled 1 millivolt Qualitative features of the loops were noted and the tracings were divided into four quadrants through the isoelectric spot Fig 1 shows the reference frame which was used for the measurements The maximum QRS and T vectors and the angle between them in each projection were measured The angle and magnitude of terminal appendages were measured in the horizontal projection only These resulted from late vectors in the right posterior quadrant The terminal appendage was measured at the point at which the QRSsÊ loop turned abruptly to return to the isoelectric spot Loops with a slight terminal curve to the right of the 90 270 degree axis were not considered to show a terminal appendage Sharp angulation in the left posterior quadrant followed by return to the isoelectric spot also was not measured as a terminal appendage The area of each quadrant of the QRSsÊ loop was determined by planimetry from the tracings of each projection and expressed as a percentage of the total QRS area for that projection The QRSsÊ loop was then divided into equal half areas by a line through the isoelectric spot in each projection as described by Pipberger This was done by planimetry by trial and error and with practice could be done fairly rapidly The angle of this axis is referred to as the half area vector angle It was considered to be the same as the maximum QRS vector in the frontal plane if the QRSsÊ loop was straight and very narrow or linear The angle between the half area vector and the maximum vector of the TsÊ loop was measured in each projection The PsÊ loops were quite small and were not studied in this project

The recording equipment included a Tektronix Type 127 power supply with two 53 54L plug in differential preamplifiers The frequency response adjustments were set at 1 kilocycle for the high range and 0 06 cycle per second for the low A Tektronix RM 32 oscilloscope was used for display of the loops The beam was interrupted 1 000 times per second and at lesser attenuations the direction of movement of

Table I Age distribution of the 72 subjects studied in this investigation

Age	Number of subjects
19-29 yr	28
30-39 yr	25
40-49 yr	10
50-59 yr	2
60 yr and over	7
Total	72

the beam was indicated by the pointed leading edges of the time markings

Results

The results of this study are presented in Table II Whenever the data provided a Gaussian distribution results are expressed as means and standard deviations If a normal distribution was not found ranges and means are given The QRS T and half area T angles in the frontal projection were clearly one half of a normal distribution when plotted as population curves with the majority of the values close to zero Standard deviations were calculated for these by the formula $\sqrt{\frac{2-N}{2N-1}}$ assuming zero as the true mean

Horizontal projection The finding of most interest was the failure of the maximum QRS vector to provide a normal distribution when graphed as a distribution curve There were two obvious groupings with a small population with maximum vectors more posteriorly oriented than in the major group (Fig 2) This was also noted with the SVEC III system by Pipberger [12] Calculations of the mean and standard deviation were performed for each of the two populations These provide usable limits when two standard deviations from each mean are employed When the frequency distribution of the half area vector angles was plotted a normal distribution was found with narrower limits

The absolute location of the TsÊ loop appeared to be a more dependable criterion than its measured relation to the maximum QRS vector The maximum QRS vector–T angle data demonstrated two overlapping distributions as would be anticipated from the spread of the maximum QRS ve

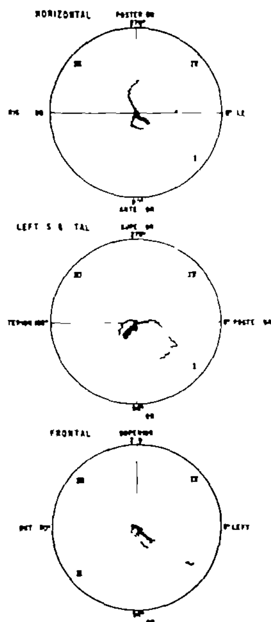


Fig. 1. Reference frame used for angular measurements in this study. A representative VCG is shown for orientation. Time markings are 1,000 per second.

angles. The half area vector T angle results were in a Gaussian curve with a much narrower range. The TsÊ loop was anterior to the maximum QRS vector in all subjects except 2 and anterior to the half area vector in all but one.

Initial anterior movement of the QRSsÊ loop, often slightly to the right, was observed *in all subjects except one*. This patient had an electrocardiogram which displayed normal R waves in the precordial leads but had a VCG with initial posterior movement. This discrepancy is not explained but Abildskov and associates[2] noted occasional deflections in the electrocardiogram which were not recorded with scalar Frank leads. The QRSsÊ loop was inscribed in a counterclockwise direction in all cases. Terminal appendages were present in 48 of the 72 subjects.

Sagittal projection. Once again there was a wide range of values for the angle of the maximum QRS vector and a peculiar frequency distribution with three peaks (Fig. 2). Means and standard deviations for the entire group and for each of the component populations provided similar 95 per cent limits (mean ± 2 standard deviation) if *the outer two sets of limits from the three* groups were compared to those for the whole. The calculation for the entire group as a single population is presented in Table II. The distribution curve for the half area vector angles was Gaussian.

The QRSsÊ loop was initially anterior and superior or inferior in all cases except one. The direction of inscription was counterclockwise in 70, and 2 others had figure-of-eight configurations with the early part of the loop counterclockwise.

Frontal projection. Much narrower ranges were found for the maximum QRS vector and T vector angles in this projection. The QRS-T angles were small. In general, there was no correlation between the angle of the maximum QRS vector and the direction of inscription of the QRSsÊ loop. However, counterclockwise inscription was not seen with loops whose maximum vector was beyond 45 degrees.

QRS areas. Wide ranges of values were found for the distribution of the percentage of QRS area in the various quadrants of each planar projection. However, certain narrow limits are considered worthy of mention. In the sagittal projection only one QRSsÊ loop had over 5 per cent of the total sagittal QRS area initially superior to the isoelectric spot. The right anterior quadrant in the horizontal projection contained no more than 7 per cent of the total QRS area of that projection in any subject.

Discussion

In this study the angle of the maximum QRS vector did not appear to be a satisfactory diagnostic criterion in the hori-

frontal and sagittal projections. The ranges of normal values were large, and the maximum QRS vector–T angles had great variability. In the frontal projection, however, narrow normal distributions of values for these parameters were found. The angle of the half area vector has been suggested by Pipberger[2] as a better measure than the maximum QRS vector angle, and when used with the SVEC III system was found to be quite close to the angle of the mean QRS vector. When the half area vector angles were measured in this study, a striking normality of distribution was found. This was in marked contrast to the data from the maximum QRS measurements in the horizontal and sagittal projections. These differences are exemplified by the VCGs shown in Fig. 3. Similarly, the half area T vector angles fell into narrower ranges in these projections than the maximum QRS vector–T angles. It is suggested that the half area vector angle has a useful place in the interpretation of the orthogonal vectorcardiogram. It is an easy measurement to perform and is much simpler than the calculation of the mean QRS axis from spatial loops or from area analysis of scalar leads.

It was hoped that measurement of the areas in various quadrants of the QRSsÊ loop in each projection would provide narrower ranges of values than those actually found. There were two places in which only a small part of the QRSsÊ loop was found normally. In the right anterior quadrant of the horizontal projection, no subject had over 7 per cent of the horizontal QRS area. This represented the earliest part of the loop. In the sagittal projection, all subjects except one had initial superiorly directed activity (in the anterior superior quadrant) of 5 per cent or less of the total sagittal QRS area. The single exception was 10 per cent. It is postulated that an increase in area beyond 5 per cent in this quadrant might correlate with the presence of small inferior myocardial infarctions which have escaped detection by other electrocardiographic and vectorcardiographic means. Other criteria for the vectorcardiographic diagnosis of inferior infarction have been used. The angle of initial superiorly directed vectors in the sagittal projection was used by Milnor and associates[14] with the tetrahedron reference frame. Qualitative criteria have been employed.[15] It is our opinion that the measurement of an area resulting from both time and voltage may be a sensitive diagnostic aid in patients whose findings are otherwise equivocal. This will require clinicopathologic proof, of course. Certainly the borderline Q wave in Lead aV_F remains an unsolved problem and one to which the orthogonal vectorcardiogram logically can be applied.

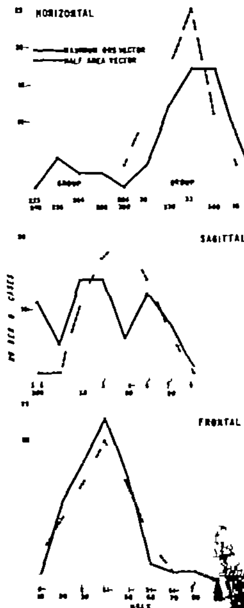


Fig. 2. Distributions of maximum QRS and half area QRS vector angles in the three projections. See text for discussion.

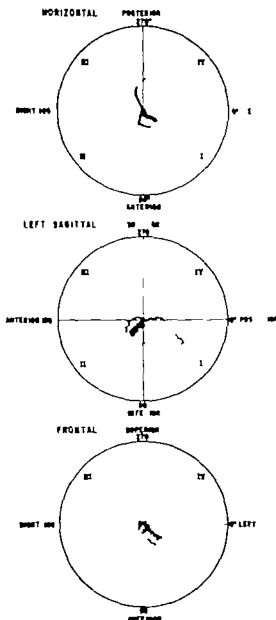


Fig 1 Reference frame used for angular measurements in this study A representative VCG is shown for orientation Time markings are 1 000 per second

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Sagittal projection Once again there was a wide range of values for the angle of the maximum QRS vector and a peculiar frequency distribution with three peaks (Fig 2) Means and standard deviations for the entire group and for each of the component populations provided similar 95 per cent limits (mean ± 2 standard deviations) if the outer two sets of limits from the three groups were compared to those for the whole The calculation for the entire group as a single population is presented in Table II The distribution curve for the half area vector angles was Gaussian

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Discussion

In this study the angle of the maximum QRS vector did not appear to be a satisfactory diagnostic criterion in the hori

spondence between VCGs obtained with different lead systems. If recently developed systems are electrically orthogonal as proposed and if the basic tenets of vectorcardiography are true, reasonably interchangeable data should be obtained with different corrected systems. The Frank system was described as giving good correspondence with the SVEC III system in a study in which leads from four orthogonal methods were interchanged.[7] After comparing the Frank, SVEC III, lead field, and Helm systems, the authors concluded that the four systems were interchangeable by current clinical standards in normal subjects and in the majority of abnormal subjects. This view was not completely acceptable to Simonson and associates,[1] who performed a comparative study of eight vectorcardiographic systems. Their analysis apparently did not include the Frank system as herein used. Pipberger[4] concluded that the SVEC III and Frank methods were close in lead strength and that angular discrepancies between the two were of minor degree only.

It was therefore of considerable interest to us to compare our results with those available from a study of the SVEC III in normal subjects.[9] In the horizontal projection, the mean for the angle of the maximum QRS vector is 4 degrees different in the two studies. The distribution curves for this parameter are similar, with separate peaks in the 330 to 15 degree segment and to the right of the 270 degree line. The results from the frontal projection suggest that the QRS-Ê loop as seen with the Frank system is located slightly higher than with the SVEC III (Table IV). The results for the T vector are close, with the greatest difference between means (7 degrees) present

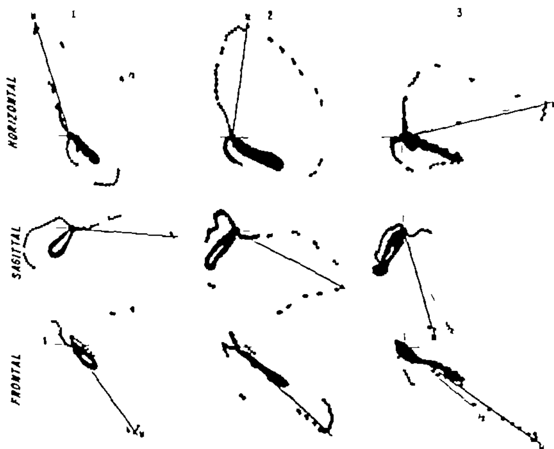


Fig. 3. Traced records from VCGs of 3 normal subjects. Widely different maximum QRS vector angles are present in the horizontal and sagittal projections. Less variation is seen when half area QRS vector angles are compared. Time markings are 1,000 per second.

*Table III Comparison of two studies with the Frank system in subjects without heart disease**

	QRS angle			T angle		
	H	S	F	H	S	F
Libretti and Zanchetti QRS and T area vector angles	290–22 (336)	13–121 (67)	10– 0 (40)	3–71 (37)	93–169 (131)	9–73 (41)
This series						
Half area QRS and maximum T vector angles	295–7 (331)	11 91 (51)	2 0 (36)	3–71 (3)	89–181 (135)	13–61 (37)

*Values [illegible] by Zanchetti and Libretti were converted to the reference frame employed in the study here reported. Means are [illegible] and the ranges tabulated are means ± 2 standard deviations. See text for discussion.

*Table IV Comparison of values from three orthogonal vectorcardiographic methods**

	QRS angle			T angle		
	H	S	F	H	S	F
Frank system (this series) Maximum QRS and T vector angles	2 7–15 (327) 2 population (see text)	339–99 (39)	7 59 (33)	5–71 (37)	89–181 (135)	13–61 (37)
SVEC-III (Pipberger[14]) Maximum QRS and T vector angles	242–44 (323) Not Gaussian	34 128 (55)	11–71 (41)	335–81 (38)	90–172 (131)	20–68 (44)
Lead field (Jordan and Beswick[7]) Main QRS loop axis and maximum T vector angle (39 selected patients)	269–333 (301)	25–81 (53)	38–86 (62)	32–92 (6)	101–173 (137)	42 78 (60)

*Values from the SVEC III and lead field [illegible] were converted to the reference frame used in the Frank series. Means are in parentheses and the ranges listed are means ± 2 standard deviations. See text for discussion.

in the frontal projection When recommended corrections were made for the originally published amplitude data for the SVEC III it was found that the maximum QRS vectors were 10 to 20 per cent larger in this study Scalar component leads were not recorded in this investigation so that accurate timing of various events in the loops was not possible for comparison with those presented by Pipberger in his analysis of the normal SVEC III results

Jordan and Beswick[1] applied a vectorcardiographic system developed from the lead field concept of McFee and Johnston to 47 healthy young men The results were described for 39 and 8 of these subjects as separate groups The 39 had VCGs which were all quite similar The smaller group of 8 had more widely varying loop parameters These workers employed the main loop axis as one measurement of the QRSsÊ loop This axis was the vector in the middle of the loop in time and apparently was very close to the maximum QRS vector A comparison of these values for their larger group and the maximum QRS vectors from this series as well as T vectors can be seen in Table IV From these data and their published photographs it appears that the lead field system employed by Jordan and Beswick produces QRSsÊ loops which are more often posteriorly and inferiorly oriented than those obtained with the Frank and SVEC III systems The means ± 2 standard deviations provide much narrower limits for their main loop QRS axis and T vector angles than the maximum QRS and T vector angles which we obtained with the Frank leads However when the half area vector angles from our study are compared with the mean manifest QRS axes from the lead field system 95 per cent limits of ap

proximately equal spread are found although with the same difference in location previously described

In a review of the literature no data were found from study of normal subjects with the corrected system designed by Helm [18]

It is obvious that any careful quantitative comparison of different lead systems requires their application to a single group of subjects However in comparing the groups previously described the differences in results with the lead field method appear to be outside the expected range of variability on the basis of testing different subject populations Whether or not there will be more variable findings with the lead field method in older subjects will require investigation

Summary

An investigation was performed with spatial vectorcardiographic recording of Frank leads in a group of 72 subjects who were free of cardiovascular disease Study of the vectorcardiograms included measurement of the angle of the half area vector in each planar projection of the QRSsÊ loop This parameter provided a narrower range of distribution in the horizontal and sagittal projections than the angle of the maximum QRS vector Information concerning QRS and T vector magnitudes is presented

The results of this study are compared with the limited information available from application of this lead system to normal subjects and with published data for the SVEC III and lead field methods

The author wishes to express appreciation to Dr H F Griswold for his encouragement and support of this project

REFERENCES

1 Libretti A and Zanchetti A Spatial patterns of ventricular repolarization in arterial hypertension Am H art J 59 40 1960
2 Abildskov J A Street W W Solomon N and Toomajian A H Clinical observations with the Frank precordial lead system Circulation 17 1069 1958
3 Sano T Ohshima H and Shimamoto T Clinical value of Burger concept as applied Frank lead system Am Heart J 57 606 1959
4 Pipberger H V and Lilienfeld L S Application of corrected electrocardiographic lead systems in man Am J Med 2 539 1958
5 Frank E and Seiden G E Comparison of limb and precordial vectorcardiographic systems Circulation 14 83 1956
6 Dower G E and Osborne J A A clinical comparison of three VCG lead systems using resistance-combining networks Am Heart J 55 523 1958
7 Langner P H Okada R H Moore S R and Fies H L Comparison of four orthogonal systems of vectorcardiography Circulation 17 46 1958
8 Burger H C van Milaan J B and Klip W Comparison of three different systems of vectorcardiography Am Heart J 57 723 1959
9 Seiden G E The normal QRS loop observed three dimensionally obtained with the Frank precordial system Circulation 16 587 1957
10 Frank E An accurate clinically practical system for spatial vectorcardiography Circulation 13 737 1956
11 Wilson F N Chairman Report of Committee on Electrocardiography American Heart Association Recommendations for standardization of electrocardiographic and vectorcardiographic lead Circulation 10 564 1954
12 Pipberger H V Evaluation of quantitative methods for obtaining mean spatial QRS vectors Circulation 16 926 1957
13 Pipberger H V The normal orthogonal electrocardiogram and vectorcardiogram Circulation 17 1102 1958
14 Milnor W R Genecin A Talbot S A and Newman E V Vectorcardiographic study of Q 3 deflection in cases of myocardial infarction and in normal subjects Bull Johns Hopkins Hosp 89 781 1951
15 Grishman A and Scherlis L Spatial vectorcardiography Philadelphia 1952 W B Saunders Company
16 Simonson E Schmitt O H and Nakagawa H Quantitative comparison of eight vectorcardiographic lead systems Circulation Res 7 296 1959
17 Jordan R C and Barnick F W Lead field scalar and loop spatial electrocardiography preliminary survey on normal adult males and comparison with other methods Circulation 18 256 1958
18 Helm R A An accurate lead system for spatial vectorcardiography Am Heart J 53 415 1957

Angina pectoris
Effect of exertion and of nitrites on precordial movements

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Previous studies from this laboratory[1] have shown that the majority of patients with angina pectoris develop a mid systolic outward movement (bulge) of the precordium at the time of pain and that this abnormal deflection either diminishes or disappears when pain is relieved by the administration of glyceryl trinitrate The present communication offers further evidence along these lines and is also concerned with additional aspects of precordial motion in such patients Some support for the concept that subthreshold exertion is beneficial in patients with coronary insufficiency will be offered as well as evidence for the presence of temporary heart failure at the time of anginal pain The effects of three coronary dilator drugs glyceryl trinitrate tablets (GTN) glyceryl trinitrate ointment (GTNO) and pentaerythritol trinitrate (PETN) on recorded precordial movements from patients with deficient myocardial oxygenation will be presented

Methods

Low frequency precordial motions (kinetocardiograms KCG) were recorded in 11 patients with typical angina pectoris Tracings were made at the end of a normal expiration by the bellows crossbar technique[2] by means of a six channel Sanborn direct writer Electrocardiographic and carotid pulse curves were secured simultaneously Each patient then exercised while recumbent by moving a 10 pound pulley weight system a distance of 8 feet every 3 seconds A critical level of exertion i e a level which would produce pain electrocardiographic evidence of ischemia or the kinetocardiographic changes previously described[1,2] as characteristic of anginal attacks was then determined for each subject This was done by using an initial exercise period of 20 seconds and then 20 second increments until one or all of the above mentioned criteria were met Such a level was termed the threshold exercise for the particular patient

After these preliminary observations the effect of a long acting nitrite was investigated the patient received either GTNO the first day and PETN the second or was given these substances in the reverse sequence The doses employed were either 1½ inches of 2 per cent GTNO spread

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tinally on the skin or 20 mg. of PETN orally. Resting and threshold exertional records were secured at ½ hour and at intervals of 1, 2, 3, and 4 hours after the drugs.

The tracings in a given individual were made from identical precordial points which had been selected during the preliminary observations as those areas which exhibited the most striking abnormalities during anginal attacks. In most instances these were the fourth or fifth left intercostal spaces in the V or V lines.

Three different precordial motions were often found to be grossly abnormal during anginal attacks and were therefore analyzed in detail. These motions were: (1) the forward movement (atrial upstroke, AU) starting shortly after the onset of the P wave of the ECG; (2) the large inward deflection (ejection downstroke, ED) beginning about the time of the carotid pulse; and (3) a large mid-systolic outward motion (bulge, B). This last motion apparently corresponds to the systolic ballooning of localized ischemic areas in the dog heart as described by Tennant and Wiggers[4] and by Prinzmetal and associates. The magnitudes of these three movements were measured in all traces and expressed as percentage of the total amplitude (TA) of the cardiac cycle. The method of measurement is indicated in Fig. 1. It should be noted that impaired ventricular contraction is indicated by a *decrease* in the ratio Ejection Downstroke/Total Amplitude or by an *increase* either in Atrial Upstroke/Total Amplitude or Bulge/Total Amplitude.

When the findings with the two long-acting drugs were compared, it was necessary to allow for spontaneous variations in the records. Although these variations are very slight in healthy persons, they may be large in patients with angina. Alterations after therapy in the size of a given motion which were less than 10 per cent of the total amplitude of the record were therefore arbitrarily considered to be without significance. An additional correction was introduced by subtracting from the number of beneficial changes the number of harmful changes which were encountered after the same drug. A change toward the typical record of healthy young adults is considered as beneficial; the opposite is deemed to be harmful. Since there is no evidence that either PETN or GTNO depresses myocardial contraction, it was assumed that these apparently harmful alterations were actually due to pure chance and that an equal number of apparently beneficial alterations might also have occurred had the drug never been administered. Although these procedures probably tend to minimize the value of each

Table I. Effect of subthreshold and threshold† exertion on the parameters studied*

Name	*Resting control* (%)	*Subthreshold exercise* (%)	*Threshold exercise* (%)
Atrial Upstroke–Total Amplitude Ratio			
1 M W	50	21	47
2 E B	38	26	65
3 C F	51	8	4
4 H A	29	22	47
5 H W	43	56	63
6 C H	4	10	2
7 A S	10	4	5
8 M D	—	—	—
9 J M	23	3	3
10 R C	11	7	11
11 J J	8	6	10
Ejection Downstroke–Total Amplitude Ratio			
1 M W	50	58	20
2 E B	53	70	2
3 C F	12	11	13
4 H A	65	63	47
5 H W	14	34	31
6 C H	25	75	4
7 A S	55	68	58
8 M D	3	13	7
9 J M	72	74	20
10 R C	27	16	28
11 J J	51	48	49
Bulge–Total Amplitude Ratio			
1 M W	77	37	60
2 F B	0	0	62
3 C F	13	8	16
4 H A	45	37	25
5 H W	8	6	16
6 C H	6	5	63
7 A S	37	28	26
8 M D	49	4	68
9 J M	3	0	4
10 R C	12	13	15
11 J J	33	10	58

*Exercise [illegible] required [illegible] pain [illegible]

†Ex[illegible] to produce [illegible]

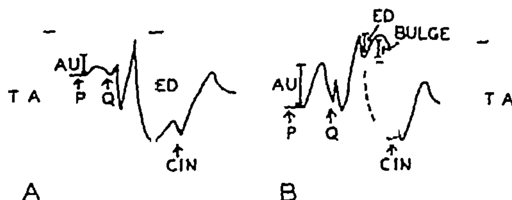


Fig 1 Comparison of the normal and abnormal relationships of the specific movements studied A and B are diagrams of typical record obtained from the apical region (Kn or V portion of the FCG) A Normal person Note the small atrial upstroke and large ventricular ejection downstroke motion Total amplitude is shown extending from the highest to the lowest recorded point of the entire complex B Angina at time of pain The abnormally large atrial upstroke the markedly decreased ventricular ejection downstroke and the mid systolic outward movement (bulge) are shown Any one or all of these may appear during anginal pain T A Total amplitude of the entire complex AU Atrial upstroke movement ED Ventricular ejection down stroke movement CIN Carotid incisural notch P I of the ECG Q Q of the ECG

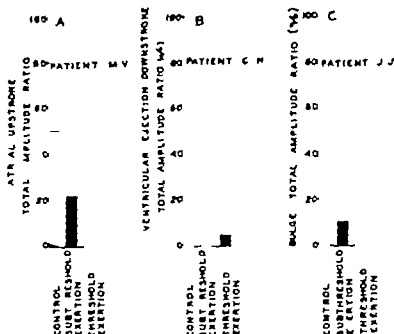


Fig 2 This figure shows the effect of subthreshold (exercise level insufficient to produce evidence of angina pectoris) and threshold (exercise level sufficient to produce objective or symptomatic evidence of angina pectoris) exertion on the three parameters studied A Patient M V with an abnormal AU/TA at rest showed a marked decrease (to within normal limits) after subthreshold exertion With greater (threshold) exertion this value approached those obtained for control B Patient C H had an increase in ED/TA of three times resting value after a level of exertion insufficient to produce evidence of angina pectoris however with an increased amount of effort which produced severe anginal pain this movement almost completely disappeared C Patient J J with a moderate bulge at rest but without pain showed a pronounced decrease in this motion after minimal exertion After greater effort a marked increase in this mid-systolic outward movement occurred Thus this figure demonstrates that degrees of effort that are insufficient to produce objective or symptomatic evidence of angina pectoris apparently have beneficial effects on precordial movements

drug it would seem that they increase the validity of the comparison between them

Results

Effect of graduated increments of exercise The normal amplitude of the atrial upstroke in relation to the total excursion is usually less than 25 per cent and always less than 33 per cent.[4,5] Four of 5 patients who showed high ratios at *rest* had lower values after *subthreshold* exertion. With further physical effort (to the point of anginal pain or ECG evidence of ischemia) the ratios tended to rise again to abnormal levels (Table I Fig 2)

After less exertion than that required to produce pain 6 patients displayed an increase as compared to resting values in the ventricular ejection downstroke–total amplitude ratio (ED TA) 2 showed a decrease and 3 showed essentially no change. With threshold exertion 5 had less than resting percentages 5 were unchanged and 1 had an increase. Thus in approximately half of the subjects mild exertion caused improvement and additional effort caused impairment of the inward movement of ejection (Table I Fig 2)

Six of the 7 patients with a definite recordable bulge (B) while at rest showed a decrease in this movement after subthreshold exertion 1 was unchanged. With greater exercise 5 increased in their bulge–total amplitude ratio 1 decreased and 1 remained the same. The other 4 patients had no definite bulge with the lesser level

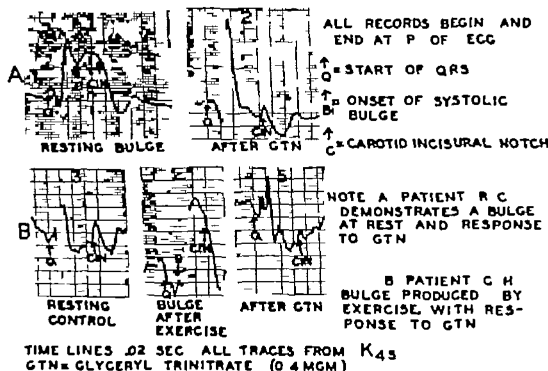


Fig 3 Paper speed 50 mm per second. Tracings taken from K regions in each of two patients with angina pectoris. 1 Record obtained from Patient R C at time when no pain and no ECG change of acute ischemia were present. *1* The record at rest shows the markedly reduced ventricular ejection downstroke movement and the prominent mid systolic outward movement (bulge) (see text). *2* Ten minutes after one sublingual tablet of glyceryl trinitrate (0 4 mg) with no detectable change in blood pressure. Note the increase in the ventricular ejection downstroke and the absence of the previous mid systolic outward movement. *B* Records obtained from Patient C H at rest after exercise and after glyceryl trinitrate. *3* The record at rest shows no mid systolic outward movement and prominent ventricular ejection downstroke movement. *4* After 1½ minutes of mild exercise sufficient to produce pain and ECG changes compatible with acute myocardial ischemia. Note the almost absent ventricular ejection downstroke movement and the large mid systolic outward movement. *5* Ten minutes after one sublingual tablet of glyceryl trinitrate (0 4 mg) with no detectable change in blood pressure. Note the similarity of this record with record *3*

Table II Alterations in precordial motions after long acting nitrites†*

Time after drug	Number of observations	Effects	Decrease in U/TA ratio				Decrease in B/TA ratio				Increase in ED/TA ratio			
			After GTNO		After PETN		After GTNO		After PETN		After GTNO		After PETN	
			Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
½ hr	10	Positive	4	3	1	?	4	6	3	1	4	6	1	2
		No change	3	5	8	7	6	4	6	6	6	1	8	5
		Opposite	0	1	0	0	0	0	0	1	0	2	1	1
1 hr	11	Positive	4	3	0	2	4	7	5	4	4	8	1	4
		No change	6	6	10	7	4	3	5	4	6	1	8	4
		Opposite	0	1	0	1	1	0	0	1	0	1	1	1
2 hr	11	Positive	4	2	0	2	4	7	3	3	2	6	2	3
		No change	4	8	9	8	6	3	6	6	6	3	5	6
		Opposite	2	0	1	0	0	0	1	0	2	1	3	0
3 hr	11	Positive	3	3	0	3	3	5	5	1	1	4	3	3
		No change	5	7	7	6	7	5	5	8	7	5	7	6
		Opposite	2	0	3	1	0	0	0	0	2	1	0	0
4 hr	11	Positive	3	2	0	3	5	5	5	3	6	7	2	3
		No change	6	6	8	5	5	3	5	7	1	2	7	5
		Opposite	1	2	2	2	0	2	0	0	3	1	1	1

*Changes of 10 per cent [illegible] of the total amplitude [illegible]

†The exercise [illegible] threshold [illegible] that which [illegible] of the drug produced clinical (pain) [illegible] electrocardiograph [illegible] S-T) [illegible] kinetocardiograph [illegible] atrial upstroke [illegible] bulge [illegible] decreased ejection downstroke) evidence of [illegible]

of effort but did have after the larger exertion

After a level of exertion less than that required to produce objective or symptomatic evidence of ischemia 10 of the 11 subjects displayed one or more objective signs of improved contractility (*decrease* in atrial upstroke or in mid systolic bulge *increase* in ejection downstroke) After threshold effort 9 exhibited worsening of one or more of these three movements as compared to the resting record and all showed impairment when the values were compared to those during the milder exercise

An occasional subject exhibited grossly abnormal precordial movements at a time when pain was absent and the ECG was normal

The similarity of the precordial movements during anginal attacks to those in patients with congestive heart failure will be considered later

The effects of nitrites The data are presented in detail in Tables II and III and are illustrated in Figs 3 4 and 5

When the immediately preceding record was abnormal sublingual glyceryl trinitrate (GTN nitroglycerin) usually produced a prompt change toward or to a normal configuration (Fig 3 Table III)

Both GTNO (nitroglycerin ointment) and PETN (pentaerythritol tetranitrate) also had pronounced effects These involved not only the prevention of pain but also the lessening or disappearance of such abnormalities as were present in the resting records and the prevention of the deterioration caused by threshold exercise in the absence of these drugs Thus the post exertional increase in the atrial upstroke was inhibited (Fig 4) the relative size of the ejection downstroke was usually increased (Fig 5) and the bulge was diminished or abolished When these abnormalities were present during the control studies they became less pronounced in each subject at some time during the 4 hour period after the two drugs

The previous clinical impression that GTNO is usually more efficacious[4] was sustained This is clearly shown in Tables II and III Because of the rigid criteria used for considering a result as beneficial these tables tend to minimize the value

of both drugs Certainly the effect of GTNO in preventing anginal pain has been more consistent than would appear from the tables In the doses employed in this study the ointment was not always superior the reverse effect was sometimes encountered (Figs 4 and 5)

The onset peak and duration of effect of the drugs varied in the different subjects, but in general appeared respectively to be at about ½ hour 1 hour and 4 to 6 hours after their administration

Discussion

The beneficial effects caused by nitrites are presumably to be ascribed to a favorable influence on the Coronary Flow/Heart Work ratio Recent reports [19] would suggest that decrease in work rather than increase in perfusion may be responsible However our studies although supplying no conclusive data on this question make it appear likely that the improvement was related to augmentation of coronary blood flow No consistent or significant decline in blood pressure was observed at the time of drug induced improvement Cardiac output was not measured during these experiments but the data of others [1] indicate no decrease after glyceryl trinitrate It seems improbable therefore that a striking decline in peripheral resistance or cardiac work occurred Furthermore the changes induced by subthreshold exercise which were directionally similar to those caused by nitrites cannot readily be explained in terms of decrease in the work of the heart

This tentative conclusion that the beneficial effects of nitrites are due to increase in coronary flow is at variance with the more direct data as obtained by the nitrous oxide method However the validity of this procedure in patients with coronary disease remains to be established In view of the proved existence of undisputed arterial collaterals [1] the venous drainage may also occur through pathways which are different from those in the normal person If so the basic assumption of the nitrous oxide

*Table III Summary of effects of nitrites on precordial movements**

Time after administration	Effect on precordial motions	Glyceryl trinitrate† (sublingual)		Glyceryl trinitrate ointment‡		Pentaerythritol tetranitrate	
		Rest	Exercise	Rest	Exercise	Rest	Exercise
3 5 min	Observations	18	18				
	Beneficial	15	17				
	Harmful	1	0				
30 min	Observations			29	28	28	25
	Beneficial			12	15	3	5
	Harmful			0	3	1	
1 hr	Observations			29	30	30	28
	Beneficial			12	18	6	10
	Harmful			1	2	4	3
2 hr	Observations			30	30	30	28
	Beneficial			10	13	5	8
	Harmful			4	1	5	0
3 hr	Observations			30	30	50	8
	Beneficial			7	12	8	7
	Harmful			4	1	3	1
4 hr	Observations			30	30	30	29
	Beneficial			14	14		9
	Harmful			4	5	3	3
Total for all observations	Observations			296		286	
	Beneficial			129		0	
	Harmful			25		24	
Excess of beneficial over harmful effects				104		46	

*Effect recorded as beneficial or harmful according to whether records became more or less like those of healthy young persons. Al[illegible] less than 10 per cent of [illegible] amplitude were considered [illegible] as no change
†As tested on subjects [illegible] records. [illegible] effect [illegible] was [illegible]
‡All tests reported [illegible] before drug was or were not [illegible]

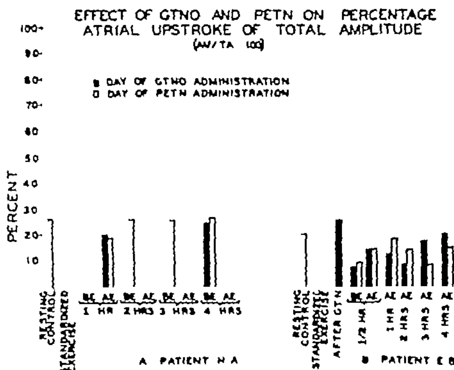


Fig. 4. Comparison of the effect of two long-acting coronary dilator drugs (GTNO and PETN) on the atrial upstroke–total amplitude ratio (see also Fig. 1) in 2 patients with angina pectoris. Resting control and standardized exercise records were made prior to the administration of each drug, and the effect of each compared was studied at hourly interval for 4 hours before and after the described exercise (see text). *A.* The percentage AU of TA remained below the standardized exercise level before and after exertion after the administration of both drugs but not below the resting control level. PETN (20 mg. in a single oral dose) produced slightly better response. *Note the low increase percentage AU of TA produced by effort when the patient was not protected by coronary dilator drugs. B.* The percentage atrial upstroke of total amplitude in Patient E. B. decreased below resting control and standardized exercise level after the administration of each drug. An approximately equal response to PETN and GTNO was noted. *Again note the large percentage atrial upstroke produced by exercise when the patient was not protected with the coronary dilator drugs.* GTNO, Glyceryl trinitrate ointment (1 inches); PETN, Pentaerythritol tetranitrate (20 mg.); GTN, Glyceryl trinitrate (0.4 mg. sublingually). *BE*, Before standardized exercise. *AE*, After standardized exercise.

method that the coronary sinus drains the left ventricle becomes unsound.

The observation that subthreshold exercise produces improvement in precordial motions, although seemingly paradoxical, is in accord with William Heberden's observations as stated in his original report.[13] We interpret it to mean that in patients with angina the coronary blood flow is initially more increased by slight exertion than is the myocardial oxygen need. With greater (i.e., threshold) effort the reverse apparently occurs.

An alternative explanation for some of the beneficial effects of light exercise in certain patients is as follows. The combination of diminished peripheral resistance[14] and augmented contractility[14] may produce increased systolic emptying with decline in ventricular end-diastolic and atrial pressures. This would cause diminished stretch and decreased contraction of the atria. This sequence would account for the observed decrease in those precordial motions which are of atrial origin. However, it is difficult to explain the effect of mild exercise in causing disappearance of the systolic bulge and in producing the increased ejection downstroke unless one assumes either (a) that the coronary flow is increased, or (b) that the myocardial oxygen consumption is diminished, or (c) that there is simultaneous marked increase in myocardial efficiency associated with

decline in the coronary venous saturation. The two latter assumptions would appear to be improbable.

Muller and Rørvik[11] have observed abrupt increase in pulmonary capillary (wedge) pressure during anginal attacks. This clear evidence of temporary left ventricular failure is supported by the present observations. The changes which we have found in precordial motions (increased atrial upstroke, large mid-systolic outward deflection, diminished inward movement of ejection) during anginal episodes are similar to those observed in patients with advanced congestive failure. These abnormalities either diminish or disappear entirely when compensation is restored. An investigation of the effects of digitalis on precordial motions during anginal attacks is in progress and will be reported at a later date.

These observations are confirmatory of previous studies from this laboratory in showing that myocardial ischemia of sufficient severity to impair the contractile function may exist in the absence of pain or electrical abnormality. The comparative value of the history, the exertional electrocardiogram, the ballistocardiogram, and the precordial movement in the diagnosis of atypical angina can only be settled by the study of a much larger group of patients.

Summary

1. In some patients with angina pectoris the precordial motions were normal at rest; in others they were grossly deranged even when pain was absent and the electrocardiogram was normal.

2. The three common abnormalities were an increase in atrial motion, mid-systolic outward bulge, and diminished inward motion during rapid ejection.

3. In 10 of 11 instances one or more of these derangements improved after exertion (subthreshold) which was considerably

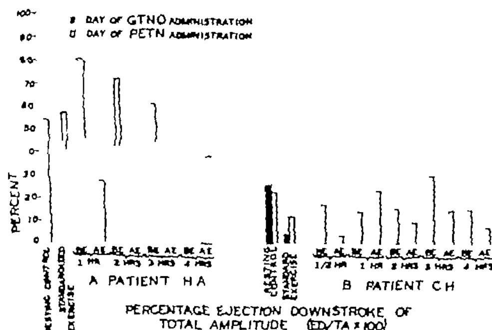


Fig. 5. The effect of exercise sufficient to produce anginal pain on the ventricular ejection downstroke–total amplitude ratio. The effects of two long-acting coronary dilator drugs GTNO and PETN are shown. *A*, Patient H. A. displayed only minimal to moderate response to GTNO but marked sustained response to PETN, the latter persisting for the entire 4 hour study. *B*, Patient C. H. received minimal protective benefit from PETN but did have a marked effect from GTNO. Note that the relative ejection downstroke percentage increased two to five times after exercise level which prior to the administration of coronary dilator drug was sufficient to produce severe anginal pain. This figure shows the individual variation in response to various coronary dilator drugs. GTN, Glyceryl trinitrate (0.4 mg. sublingually); GTNO, Glyceryl trinitrate ointment (1½ inches); PETN, Pentaerythritol tetranitrate (20 mg.); *BE*, Before standardized exercise; *AE*, After standardized exercise.

less than that required to produce pain or other evidence of myocardial ischemia

4 More strenuous (threshold) exertion caused exaggeration of one or more of these abnormalities when they had been previously present and induced their appearance when previously absent

5 Sublingual glyceryl trinitrate caused these distortions to decrease markedly or to disappear in 32 of 36 trials

6 Glyceryl trinitrate ointment and pentaerythritol tetranitrate tablets both exerted a beneficial effect in tending to diminish or abolish abnormal motions Although the ointment was usually the more effective drug the oral preparation appeared to be better in some instances

7 Data concerning the onset peak and duration of action of these two drugs are presented

8 The findings offer indirect evidence for the increased coronary flow in contrast to the diminished cardiac work hypothesis as to the mechanism responsible for the improvement produced by nitrites

9 In so far as can be judged from precordial motions the temporary changes in myocardial contraction during anginal attacks are similar to those which occur during congestive heart failure and disappear as improvement occurs

REFERENCES

1 Harrison T R and Hughes L Precordial systolic bulges during anginal attacks T A Am Physicians 71 174 1958
2 Harrison T R Some clinical and physiologic aspects of angina pectoris Bull Johns Hopkins Hosp 104 275 1959
3 Eddleman E E Jr Willis K Reeves T J and Harrison T R The kinetocardiogram I Method of recording precordial movements Circulation 8 269 1953
4 Tennant R and Wiggers C J Effect of coronary occlusion on myocardial contraction Am J Physiol 112:351 1935
5 Prinzmetal M Schwartz L L Corday E Spritzler R Bergman H C and Kruger H E Studies on the coronary circulation VI Loss of myocardial contractility after coronary artery occlusion Ann Int Med 31 429 1949
6 Harrison T R Lowder J A Hefner L L and Harrison D C Movements and forces of the human heart V Precordial movements in relation to atrial contraction Circulation 18 82 1958
7 Ingram R H Kinetocardiographic findings in normal subjects after a standard exercise procedure Thesis presented to the Faculty of Yale University School of Medicine 1960
8 Harrison T R Principles of internal medicine New York 1958 McGraw Hill Book Co Inc
9 Gorlin R Brachfeld N MacLeod C and Bopp P Effect of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricular work Circulation 19 705 1959
10 Brachfeld N Bozer J and Gorlin R Action of nitroglycerin on the coronary circulation in normal and in mild cardiac subjects Circulation 19 697 1959
11 Muller O and Rørvik K Haemodynamic consequences of coronary heart disease with observation during anginal pain and on the effect of nitroglycerin Brit Heart J 20 302 1958
12 Blumgart H L Schlesinger M J and Davis D Studies on the relation of the clinical manifestations of angina pectoris coronary thrombosis and myocardial infarction to the pathological findings Am Heart J 19 1 1940
13 Heberden W Commentaries on the history and cure of disease London 1802 T Payne
14 Hamilton W F Role of the Starling concept in regulation of the normal circulation Physiol Rev 35 161 1955
15 Sarnoff S J Myocardial contractility as described by ventricular function curves observations on Starling's law of the heart Physiol Rev 35 107 1955
16 Skinner N S Jr Kinetocardiographic findings in patients with congestive heart failure and the effect of digitalis (In preparation)

Case reports

An unusual type of intermittent A-V dissociation in acute rheumatic myocarditis

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Involvement of the A-V node has been well documented in cases of active rheumatic myocarditis. The inflammatory and vascular changes that are produced in this region may give rise to a variety of arrhythmias, and among these A-V dissociation is one of the most interesting. The case to be presented illustrates some problems of interpretation that may arise when in acute rheumatic fever A-V junctional tissues are involved by the pathologic process and become the site of an additional ectopic pacemaker. Detailed analysis of the electrocardiograms provided an opportunity (a) to study mechanisms of intermittence of A-V dissociation and of temporary synchronization ("accrochage") of atrial and ventricular action and (b) to reappraise the role of ventricular fusion beats in the distinction between ectopic rhythms of supraventricular origin and those of ventricular origin.[1]

Case report

J. H., a 15-year-old Negro boy, entered the Cook County Hospital on April 23, 1960, complaining of pain and swelling of the right ankle and precordial pain which had been present for the previous 4 days. The patient stated that he was perfectly well until 1 month prior to admission, at which time he had a sore throat. He did not receive any medication for his pharyngitis at that time. Ten days prior to admission he developed headache and fever; 3 days later he noticed pain and swelling (migratory in nature) of the left knee, left ankle, and both elbows. Two days prior to admission he had a recurrence of sore throat and developed precordial chest pain.

Physical examination. The patient was a well-nourished, well-developed young Negro boy in no acute distress. His temperature was 101° F. orally; the pulse varied from 70 to 80 per minute; respirations were 16 per minute; and blood pressure was 130/ 0 mm. Hg. No rash was noted on the skin; the pharynx was not injected. The heart was of normal size. The heart tones were loud, and a diastolic gallop was present. A Grade 2 systolic ejection murmur was heard at the pulmonic area, preceded by an early systolic click. A Grade 1 apical mid-diastolic rumble was also present. No variation in the first heart tone was noted at the time of admission. Tenderness and swelling were present in the region of the right ankle. The rest of the physical findings were noncontributory.

Laboratory data. A blood count showed 3,460,000 erythrocytes, hemoglobin of 9.8 Gm., 10,400 white blood cells of which 65 per cent were polys, 20 per cent bands, 11 per cent lymphocytes, and 4 per cent monocytes. Sedimentation rate was 56 mm. The urinalysis was normal. Throat and blood cultures and three lupus erythematosus preparations were all negative. Electrolytes, fasting blood sugar, and blood urea nitrogen were not remarkable. Antistreptolysin O titer and C-reactive protein at the time of the patient's admission were 250 Todd units and 4 plus, respectively.

Roentgenographic examination of the chest revealed the heart and lungs to be within normal limits. The electrocardiograms are discussed below.

Hospital course. The patient was started on 100 mg. of cortisone three times a day, and within 1

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hours after admission all pai i the joi t and swell ing had disappeared Within 3/ hours the patie t became afebrile and remaine l throughout his entire ho pital course The patie t a lso started on da ly procaine penicillin 600 000 units nd at the end of 2 week w place l on Bicillin After 2 week f ther py the se limentation rat had dropped to 14 mm and the abnormal auscultatory findings of the heart d appe red R peat nt streptolysin O titer and C reactiv protein t th time re still 250 and 1 plu The final diagno is was rheumatic fev with active myocarditis

Electrocardiograms

The first electrocardiogr im was obt ined before therapy w is st irted The only ab normality noted w is disturbance of rhythm illustr ited in Fig 1 The sinus r ite v iries between 65 and 88 per minute and there are three types of ventricular complexes all with i norm il QRS dur ition of 0 08 second The first with small QRS and in inverted T w ive is linked to P waves t a const int prolonged P R interval of 0 24 second (first three be it in strip *a* and second and third be it in strip *d*) These occur during atri l rate of 77 to 88 and represent fully condu t d inus im pulses The second type with large QRS complexes and upright T w ves has no c nstant relation to P w ives the l itter either precede QRS at i short v iriable dis t ince (as in strips *a* and *c*) or coincide with it (is in strip *b*) These represent impulses of in accelerated subsidi iry p icem iker which is di ch irging at i precisely regular r ite of 67 and interferes in the A V junc tion with sinus impulses whenever the r ite of the l itter has slowed to 68 or more The result is in isorhythmic A V dissocia tion The third type (fifth to seventh be its in strip *d*) follows P w ves at the same P R interv il is the sinus beats but is intermedi ate in sh ipe between the other two types These beats occur during sinus rates of 70 or 71 and represent ventricular fusion beats due to interference of sinus and ectopic im pulses within the ventricles Their signifi cance with reg ird to the location of the ectopic p icemaker is discussed below

On the following D y isorhythmic A V dissoci ation w is still present but at a slower rate of 58 (Fig 2 *a*) On the third hospital day the sinus rate v iried between 44 and 65 but the accelerated ectopic activity had subsided (Fig 2 *b*) Consequently ill sinus impulses were conducted at a prolonged P R of 0 24 second Subsequent electrocar diograms showed gradual regression of the A V conduction disturb ince and on the eleventh hospital day the tracing w is nor mal with i P R of 0 14 second (F 2 *c*)

This series of electroc irdiogr ims re ve iled therefore i first degree A V block at first in conjunction with an intermittent and isorhythmic type of A V dissociation induced in i sinus arrhythmi i by tempo r iry icceler ition of i subsidiary ectopic pacemaker The loc ition of the l itter is discussed below Both these abnorm ilities dis ippe ired with clinic il improvement of the p itient

Discussion

The term *A V dissociation* in its bro idest sense comprises disturb inces of c irdi ic rhythm ch ir icterized by independent ac tion of atria and ventricles Its sever il v irietie are subject to different cl issifica tions depending on whether they are viewed from the standpoint of *duration* of *completeness* or of the *mechanisms* responsi ble for the disturb ince[3] Thus in i given record the A V dissoci ition m iy be per sistent or it may alternate with longer peri ods of norm il rhythm (intermittent v i riety) On the other hand persistent as well as intermittent A V dissoci ition m iy be incomplete or complete in th it a regul ir sequence of the ectopic be its m iy or m iy not be disturbed by atri il impulses sporadi c illy traversing or penetrating to the point of origin of the ectopic pacemaker (ventricul ir c iptures) Finally from the viewpoint of mechanisms persistent or in termittent complete or incomplete A V dissoci ition may be the result of either (a) delay in irriv il of the atrial impulses or (b) e irly discharges of a subsidiary cen ter The former passive mechanism may result from sinus bradycardia or in S A or A V block the latter active one occurs in a paroxysmal and nonparoxysmal variety distinguished by the type of onset and termination as well as by the degree of ac celeration of ectopic impulse formation

In acute rheumatic fever the most com mon cause of A V dissociation is i non paroxysm il A V nodal tachycardia It is a highly significant finding and has the same clinical connotations with regard to in volvement of the myocardium specifically

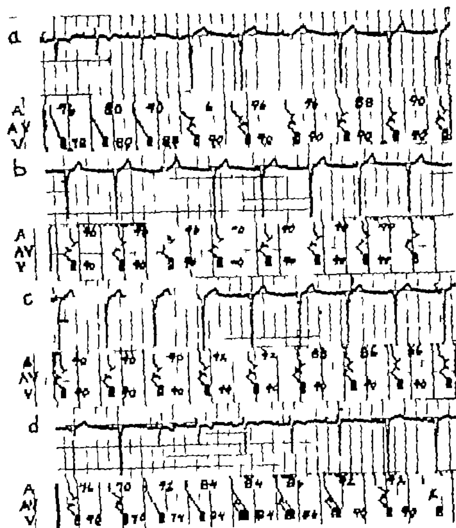


Fig. 1. Electrocardiogram at the time of admission (April 23, 1960). Segments of a consecutive portion of a long Lead V with only a few beats omitted between the individual strips. The symbols in the diagrams are conventional. The solid blocks under V represent ventricular activation by sinus impulses; the shaded blocks, activation by ectopic impulses which originate within the A-V node and use a preferential path to the ventricles; their combination indicates ventricular fusion beat. Discussed in text.

the A-V node by the underlying rheumatic disease as does a prolongation of the A-V conduction time. These two functional disorders may or may not be associated. They differ in that, as a rule, acceleration in nodal impulse formation is more transient than the delay in A-V conduction. Whether under these circumstances the A-V dissociation is persistent or intermittent, or is complete or incomplete, will depend on the degree of nodal acceleration relative to the rate and rhythmicity of the sinus node and the state of refractoriness of the A-V node. Since in nonparoxysmal tachycardias acceleration of ectopic impulse formation is only moderate and remains within the range of sinus rhythms, there is frequently transient or persistent synchronization of the two rhythms. This phenomenon is known as *isorhythmic dissociation* or *accrochage*. There is reason to doubt whether the mechanism of accrochage as conceived by Segers is actually demonstrable in the human heart. Grant reproduced the phenomenon experimentally and demonstrated a "pull in" of two coupled oscillators operating originally at two different rates. He concluded that such

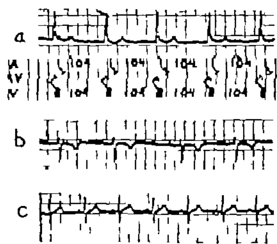


Fig. 2. Electrocardiogram after therapy. Discussed in text. *a,* Lead III taken on April 24. *b,* Lead V taken on April 25. *c,* Lead I taken on May 8.

physical principles can be applied to explain various manifestations of nodal arrhythmia including accrochage. However, it is possible that temporary synchronization may simply be the result of chance acceleration of ectopic impulse formation to but not beyond the range of a pre-existent arrhythmia of the sinus pacemaker. Such an interpretation can readily be applied to the present case since the apparent linkage of the two pacemakers (Fig. 1 *b*) is immediately broken as soon as the sinus rate speeds up (Fig. 1 *d*).

The interpretation of complexes 5, 6 and in *d* of Fig. 1 as being ventricular fusion beats is based on the following facts: (a) They are intermediate in contour between the sinus and ectopic beats. (b) These beats occur exclusively at the time of sinus slowing when the appearance or disappearance of ectopic beats can be predicted. (c) The cycle of these beats is either equal to or only 0.04 second shorter than the regular ectopic cycle. (d) Each of these beats is preceded by a P wave with the same P-R interval as seen in the normally conducted beat. Yet the identification of these beats as ventricular fusion beats creates one difficulty, namely, that of establishing the location of the ectopic pacemaker—the most intriguing aspect of the tracing.

Ventricular fusion beats are the result of interference at ventricular levels of two activation waves.[3] Obviously, this cannot take place if the two impulses share a common path through the A-V junction. At least one must originate below the bifurcation of the common bundle or else reach the ventricles over a devious path. Hence, the occurrence of ventricular fusion beats in an ectopic rhythm with prolonged and bizarre ventricular complexes can ordinarily be considered as strong evidence of a ventricular location of the ectopic center.[3] However, in the application of this criterion to the case presented, the problem arises of accounting for the normal QRS duration of the ectopic beats. This dilemma could be resolved on the basis of two alternative assumptions: (a) the ectopic impulses originate in the A-V junction but use a preferential pathway in reaching the ventricles or (b) they originate within the ventricular septum about midway between the two bundle branches.[3] Either of these two mechanisms could conceivably result in aberrant ventricular beats with a normal QRS duration. We are unable to distinguish conclusively between these two possibilities but we favor for empirical reasons the first interpretation (indicated in the diagrams to Fig. 1), since acceleration of A-V nodal and not ventricular impulse formation is the common manifestation of involvement of the heart muscle in an acute rheumatic process, as was present in this case.

It should be emphasized that this recognition of the occurrence of ventricular fusion beats in the face of a supraventricular ectopic rhythm does not of necessity conflict with the foregoing statement concerning the crucial role of fusion beats in the distinction between ventricular and supraventricular ectopic beats. This criterion appears to be diagnostic if the QRS duration of ectopic beats of questionable origin exceeds 0.12 second.

Summary and conclusions

1. We have reported a case of active rheumatic myocarditis which was revealed by two functional manifestations of a pathologic process involving the atrioventricular junctional tissue: a nonparoxysmal A-V nodal tachycardia and impairment of A-V conduction which resulted in intermittent isorhythmic A-V dissociation.

2. A-V dissociation always started with slowing of the sinus pacemaker and

promptly disappeared with its acceleration Temporary synchronization of atrial and ventricular action appeared to be a chance phenomenon which depended on a sinus arrhythmia rather than the result of a pull in (accrochage) of two rhythms dif fering in rate a mechanism implied by others

3 The ventricular complexes of the ectopic rhythm differed markedly from those of sinus origin in contour but not in QRS duration Considering the known af finity of the rheumatic process to A V junc tional tissues we assume that the site of this ectopic pacemaker was above the bi furcation of the common bundle probably in the A V node and we attribute the aberration in contour to a preferential conduction path to the ventricles

4 At the transition of the undisturbed sinus rhythm into A V dissociation and vice versa there was competition between sinus and ectopic impulses for control of the ventricles which caused ventricular fusion beats The significance of the latter in the difficult distinction between supra ventricular and ventricular beats is re evaluated

REFFRENCES

1 Gross L and Fried B M Lessons in the auriculoventricular conduction system occurring in rheumatic fever Am J P th 12 31 1936
2 Segers M Les phénomènes de synchronisation au niveau du coeur Arch internat physiol 54 87 1946
3 Katz L N and Pick A Clinical electrocard ography Part I The arrhythmias Philadelphia 1956 Lea & Febiger
4 Schott A Atrioventricular dissociation with or without terference Prog Cardiovas Di 2 444 1960
Pick A nd Dominguez P Nonparoxysmal A V nodal tachycardia Circulation 16 1022 1957
6 Marriott H J L Atrioventricula synchroniza tion and accrochage Circulation 14 38 1956
7 Grant R P The mechanism of A V arrhy thmias w th an electronic analogue of the human A V node Am J Med 20 334 1956
8 Pick A and Langendorf R Differentiation of supra entricular and entricular tachy cardias Prog Cardiovas Dis 2 391 1960
9 Pick A Aberrant entricula conduction of escaped beats preferential nd accessory path w y in the A V junction Circulation 13 702 1956

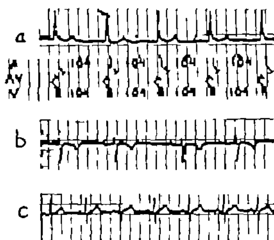


Fig 2 Electrocardiograms after therapy Discussed in text a Lead III taken on April 24 b Lead V taken on April 25 c Lead I taken on May 8

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Summary and conclusions

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2 A V dissociation always started with slowing of the sinus pacemaker and

Methods

All chemical determinations were done in duplicate Methods used were Ca and Mg—photoelectric titration with complexon III) Na and K—flame photometer total protein—biuret method protein fractions—according to Majoor [6]

ECG tracings were made with a Sanborn Viscocardiette The Q T interval was measured from the beginning of the Q to the end of the T wave with an accuracy of within 0 01 second The values subsequently given for the Q T intervals represent the average of 4 to 6 measurements on consecutive cardiac cycles of Lead I The differences between the Q T intervals of the various leads were in no instance larger than 0 02 second

Case histories

Case 1 Patient K H a 28 year-old ma went to Surinam (West Indies) in September 1956 On November 11 during the homeward journey he had a severe attack of tropical malaria followed by an acute anuria Because of hyperkalemia and lung edema peritoneal dialysis as performed elsewhere the application of cuffs around the thighs for 36 hours having had no effect

Hyperkalemia nd lung edema disappeared but the patient remained apathetic nd the anuria persisted

On December 2 the third day after the peritoneal dialysis paresis of the legs became manifest together with absence of the tendon reflexes This could not be explained by the level of plasma potassium (5 4 mEq /L) No sensory disturbances were noted The ECG showed sinus tachycardia with definite prolongation of the Q T interval hypocalcemia was suggested by Dr A P M Verheugt the consulting cardiologist The blood pressure which had *been normal started to drop and* that same evening t 5 P M the patient was transferred to our department in state of shock with blood pressure of 80/60 mm Hg regular pulse rate of 105 and pronounced triple rhythm The heart was not enlarged on percussion and there ere no signs of lung edema or peripheral edema Chvostek sign was absent the pare is of the lower limbs had become marked

Because of the peculiar flaccid paresis of the lower limbs 25 mg of thiamine chloride intramuscularly as gi en tentatively t 6 M Blood analysis how ever confirmed the diagnosis of Dr Verheugt nd revealed severe hypocalcemia (2 1 mEq /L) as ell as hyperphosphatemia (18 mg per cent) and uremia (4 Gm /L) The other electrolytes were not noticeably abnormal (Fig 1 *Observation 1*)

It was then decided to try the intravenous administration of Ca and an infusion of Ca gluconate (44 mEq of Ca in 510 ml of 5 per cent glucose) was started t 11 P M The beneficial effect on the plasma Ca ECG blood pressure and triple rhythm show in Fig 1 *Observation 1* and will be discussed later

Parallel with the improvement in the level of plasma Ca acti movement of the legs al returned The tendon reflexes could be elicited again 2 hours after the tart of the administration of Ca

In the course of the following day d uresis gradually et in and ultimately the patient recovered completely N further thiamine was gi en Administration of Ca however had to be continued in qua tities up to 80 mEq daily for another 2 *eeks in order to prevent hypocalcemia N further* circulatory or neurological abnormalities ere noted The effect of peritoneal dial sis and the course of the renal failure this patient ha been reported elsewhere The moderate hypocalcemia (3 5 mEq /L) which existed before dialysis was aggra ted presumably by low concentration of Ca ion in the irrigation fluid due to precipitation of CaCO The rise in the plasma phosphate during the day following the dialysis induced further decrease the plasma calcium

Case 2 Patient St a 22 ear-old married woman who had history of tonsillitis and acute glomerulonephritis 4 years previously mitted ho pital elsewhere in November 1958 because of increasing compla t of omiting nd epi taxis Severe uremia (blood urea 4 000 mg /L) w th oemia resulting from chronic glomerulonephritis as diagnosed At that time the blood pressure was 170/120 mm Hg

Vomiting persisted and on Dec 27 1958 she as admitted to our department

The blood pre sure was then 110/80 mm Hg which contrasted sharply with the hypertension found previously The pulse rate was 80 to 90 nd *regular There were no signs of dehydration* but on the contrary slight edema This could not be due to low content of albumin (lbumi 31 Gm /L total protein 58 Gm /L)

The heart was not enlarged on percus ion and there was no triple rhythm Chvostek sign as positive but there were no ther neurological abnormalities and no history of manifest tetany There was no paresis of the limbs and the patient although ill was mentall alert The ECG showed sinus *rhythm with prolongation of the Q T interval*

The blood chemistry (see *Observation 2* Fig 1) revealed severe uremia with pronounced hypocalcemia (2 3 mEq /L) and hyperphosphatemia (23 6 mg per cent) The level of potassium as only slightly rai ed (5 mEq /L) and there was mild metabolic acidosis (HCO concentration 16 0 mEq /L)

The creatinine clearance as extremely low (2 t 3 ml /min) nd the diuresis remained fixed t about 1 l ter in 24 hours with an excretion of lbumin of 4 Gm daily The excretion of Ca was not determined

Immediately after the patient was admitted to the hospital an inf sion of calcium gluconate (44 mEq of Ca in 600 ml of 5 per cent glucose) was tarted Thi resulted in normalization of the ECG and concomitant rise in blood pressure The general condition improved considerably The correlation with the level of plasma calcium is show in Fig 1 *Observation 2*

Clinical improvement however was temporary and after 2 day the plasma calcium had dropped to the me low level the blood pressure had fall

Fig. 1. Graphic representation of observations in Patient K. H. and Patient St. The normal range for the Q-T interval was taken from the *Electrocardiographic Test Book* of the American Heart Association. The mean normal values indicated for the magnesium and potassium plasma are the values found for normal persons in our department. For Ca this value is corrected for the deviation of total plasma protein in our patients from 70 Gm./L. using the formula of McLean and Hastings.

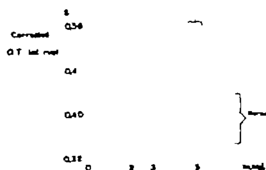


Fig. 2. Correlation between the concentration of calcium in the plasma and the corrected Q-T interval (Kissane and co-workers[4]). Solid dots: Patient K. H. (*Observation 1*). Open dots: Patient St. (*Observations 2 and 3*). The broken line indicates the general trend and has no statistical significance. The normal range for corrected Q-T interval in adults was taken from the *Electrocardiographic Test Book* of the American Heart Association.[10]

and the ECG again revealed the typical abnormality notwithstanding the administration of 20 mEq. of calcium and a large amount of fluid (2,500 ml. of 20 per cent glucose) intravenously on December 28. A second rapid infusion of calcium gluconate (44 mEq. of Ca in 220 ml. of 5 per cent glucose) again had a beneficial effect (see Fig. 1, *Observation 3*). This time Chvostek's sign was repeatedly looked for and was found to disappear gradually with the normalization of the plasma calcium.

The patient was treated with calcium gluconate and infusions of glucose, vitamin D, oral calcium, Aluminox (which is 5 per cent Al(OH)3 gel), and low protein diet but the uremia rapidly increased and she died on Jan. 19, 1959. At autopsy a severely contracted right kidney and a hypoplastic left kidney with hypoplastic renal artery were found.

An extremely high concentration of inorganic phosphate in the plasma in combination with insufficient compensatory activity of the parathyroid glands might have been responsible for the persistent hypocalcemia in this patient.

Effect of administration of Ca on blood pressure ECG and blood chemistry

In Fig 1 the effect of infusion of Ca gluconate on the clinical signs blood pressure Q T interval and blood chemistry is shown In all three observations a correlation exists between the level of Ca in the plasma Q T interval and blood pressure The blood pressure became stabilized at the normal level for the patient as soon as the plasma Ca had become normal At that moment the Q T interval had also come within a normal range in all three observations about 20 mEq of Ca had been given until then The rise in plasma Ca above the normal level seen during *Observation 2* is accompanied by a continuing decrease in the Q T interval but not by a further increase in blood pressure

In Fig 2 the concentration of plasma calcium and the Q T interval (corrected to a heart rate of 60 per minute using the nomogram of Kissin and co workers[9]) are correlated Only with plasma concentrations below 3 5 mEq /L did the Q T interval become significantly prolonged

Fig 3 shows serial electrocardiograms of the patients It should be noted that the prolongation of the Q T interval is due to a lengthening of the S T segment In Patient K H an inverted T wave which was seen in Leads I II and aV$_L$ became less negative during infusion of calcium in Leads III aV$_R$ and aV the T waves were positive tending to flatten during infusion of calcium In the second patient the T waves stayed positive

There was initially in all three observations a slight to moderate hyperkalemia During administration of Ca changes in plasma potassium were seen but these showed no constant pattern during the first observation a decrease of 0 8 mEq /L occurred in the second observation no change was seen whereas during the third observation a decrease of 1 mEq /L occurred The decrease must be attributed to the glucose administered

The concentration of magnesium which was slightly elevated in Patient K H remained constant during the infusions of Ca

No significant changes were observed in the content of bicarbonate in the plasma (Fig 1 *Observations 1 2 3*) nor in the pH of the venous blood drawn from the resting forearm (Fig 1 *Observation 3*) The latter value was well within normal range

Total concentration of protein in the plasma was only slightly below normal and did not change during the observation period

Discussion

Before considering the circulatory and electrocardiographic changes we will comment briefly on the neurological findings The flaccid paresis of the lower limbs with absence of tendon reflexes which was observed only in Patient K H is at variance with the known effects of hypocalcemia and might even be called paradoxical The fact that the administration of Ca promptly restored normal movement and tendon reflexes nevertheless suggests that the hypocalcemia was partially responsible A contributory mechanical factor may have been the application of cuffs around the thighs for 36 hours at a pressure of 60 mm Hg In Patient St Chvostek s sign was positive but there was no manifest tetany although the concentration of Ca ion in the plasma must have been very low Strawitz and associates[1] and Clowes and Simeone also observed no signs of tetany notwithstanding the low levels of Ca ion in the plasma We have no explanation for this lack of nervous hyperexcitability

It is improbable that the administration of 25 mg of thiamine chloride intramuscularly was responsible for the sudden and lasting improvement in Patient K H 6 hours later The patient had always had an adequate diet and was not an alcoholic The neurological and circulatory disturbances developed within 2 days without an evident increase in demand for thiamine Finally although shock and prolongation of the Q T interval have been described in cases of thiamine deficiency the improvement both in the circulation and neurological signs occurred in the course of 2 hours and in close correlation with the change in the level of Ca in the plasma (Fig 1 *Observation 1* and Fig 2)

In view of the observation made in Patient St who received only calcium a direct relation seems to exist therefore between hypocalcemia prolongation of the

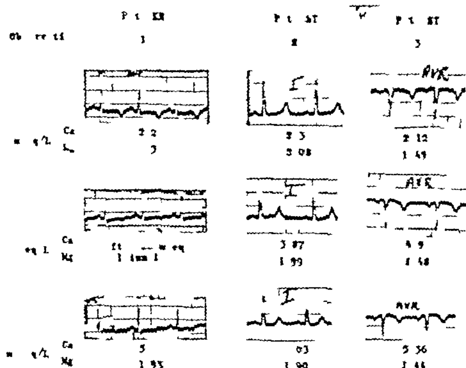


Fig. 3. Serial electrocardiograms which show normalization of the Q-T interval during administration of calcium. *Observation 1*, Lead I; *Observation 2*, Lead I; *Observation 3*, Lead V_R.

Q-T interval and hypotension, and it would appear that the low level of Ca in the plasma—which in the absence of significant abnormalities in the plasma proteins and pH indicates a very low concentration of Ca ion—was responsible not only for the ECG changes but also for the decrease in blood pressure.

From the fact that manifest shock concomitant with triple rhythm developed in Patient K. H., and that both disappeared as the plasma Ca rose to normal levels, it would appear that the effect of hypocalcemia on the arterial blood pressure is due to a decrease in the force of cardiac contraction and not to a diminished peripheral vascular resistance. The amount of fluid administered parenterally is too small to explain the increase in arterial pressure. The level of potassium in the plasma was slightly elevated but did not show a correlation with the increase in arterial pressure and can therefore not account for it.

The outstanding electrocardiographic abnormality was the prolongation of the Q-T interval; such prolongation was first described by Carter and Andrus in 1922 and subsequently by many other authors.[?] It is due to a lengthened S-T segment and is now considered to be characteristic of hypocalcemia. The fact that in our patients the Q-T interval became significantly prolonged only at concentrations of Ca below 3.5 mEq./L. (Fig. 2) is in agreement with observations made by others.[?,?]

Bellet occasionally found inverted T waves during hypocalcemia. These became less negative after the administration of Ca. Similar alterations in the T wave were seen in Patient K. H. (Fig. 3).

With the exception of that cited in the introduction, the clinical literature on hypocalcemia does not mention observations on cardiac function or arterial pressure. But experiments on the isolated heart support the assumption that hypotension in cases of hypocalcemia is caused by a diminished force of cardiac contraction.[?] Under standardized conditions the force of contraction of the frog heart can be used as a measure of the concentration of Ca ion in the perfusion fluid, and it is interesting to note that the isolated frog heart is most sensitive to small changes if the

concentration of Ca is low. At normal and high concentrations changes in the level of Ca ion do not appreciably influence the force of contraction.[21-27]

The same pattern can be observed in *Observation 2* Fig. 1. The most impressive rise in blood pressure occurred immediately after the concentration of Ca started to rise and an increase of the level of Ca in the serum above the normal level did not further increase the arterial blood pressure.

The observations of Straswitz and associates[1] and Clowes and Simeone[2] and our observation can be said to demonstrate a digitalis-like action of Ca on the force of cardiac contraction in cases of hypocalcemia. It is of interest therefore that other workers found evidence for a synergistic or additive action between Ca and digitalis glycosides in experiments on the isolated heart,[22-24] on intact animals,[25] and in clinical observations.[26] The evidence put forward in the publications just referred to is often too circumstantial or lacking in facts and quite a number of authors have refuted the proposed synergistic or additive action between Ca and digitalis glycosides on the grounds that an increase in the level of Ca in the plasma above the normal level does not significantly increase the toxicity of the digitalis preparations administered.[28]

We think that in these experiments—as in the experiments on the isolated frog heart—the absolute level of plasma Ca or to be more accurate Ca ion is decisive. This is clearly shown in the publication of Friedman and Bine,[25] who from their experiments on the embryonic duck heart concluded that Ca had no influence upon the action of a digitalis glycoside. However, when Ca was omitted from the perfusion fluid the hearts were significantly more resistant to the digitalis glycoside used than when the perfusion fluid contained about 4 mEq./L. of Ca. An increase in the content of Ca above that level had no effect. Rohrer[27] demonstrated a similar dependency of the digitalis effect on the absolute level of Ca in the isolated frog heart.

It seems therefore that a similarity exists between the effect of digitalis and of Ca on the heart and Szent-Gorgyi[2] suggested that this is due to the fact that Ca ... the mechanism responsible for transport of potassium into the cell in the same manner as do the cardiac glycosides.

Whether this is true or not,[27] it has long been known that the effect of Ca on isolated heart muscle is influenced by the concomitant concentration of potassium; diminished force of contraction is seen only with hypocalcemia if the concentration of potassium is at least normal. If the concentration of potassium in the perfusion fluid is lowered concomitantly with the concentration of Ca, the force of contraction of an isolated frog heart remains normal.[29]

The 4 patients with severe hypocalcemia and hypotension mentioned by Clowes and Simeone[2] all had a slightly elevated potassium. The same was found in our patients. The patient observed by Merrill et al.[3] had a moderate hypocalcemia but was frankly hyperpotassemic. It will be interesting to study circulatory changes after the administration of Ca and potassium respectively in patients who have both a low level of Ca and potassium in the plasma.

Summary

Three observations in 2 uremic patients with severe hypocalcemia are described.

1. Besides prolongation of the Q-T interval, severe hypotension was found.

2. During intravenous administration of calcium the blood pressure rose and the Q-T interval was normalized concomitant with the increase of the concentration of plasma calcium to its normal level; when in the second patient the concentration of Ca again diminished, hypotension and prolongation of the Q-T interval reappeared.

3. In the first patient a triple rhythm was present during hypocalcemia but disappeared during administration of Ca. A flaccid paresis of short duration of the lower limbs existed but also disappeared completely during administration of Ca. Chvostek sign was consistently negative.

4. The conclusion is that in these cases hypocalcemia was responsible for the hypotension probably by decreasing the force of cardiac contraction. The slightly elevated level of potassium found in all three observations may have been a contributory factor.

5 Since others have made similar observations after massive transfusion of citrated blood and during major operations the possibility of hypocalcemia should be considered in patients with hypotension refractory to adequate transfusion The finding of a prolonged Q T interval due to lengthening of the S T segment is then of diagnostic importance since the classic neurological signs of hypocalcemia may be absent

Addendum

After this paper had been submitted for publication a fourth observation was made in Patient Fr a 52 year old woman who suffered from chronic renal insufficiency which probably resulted from pyelonephritis

When she was first admitted in 1959 the nephritis was found to be of the salt losing type Arterial pressure varied between 170/110 and 210/130 mm Hg plasma sodium between 118 and 135 mEq /L and endogenous creatinine clearance between 5 and 11 ml /min Plasma calcium then was 3 5 mEq /L

In August 1960 she was readmitted in a severely overhydrated state with an arterial pressure of 160/100 mm Hg With the intake of fluids and salt restricted the overhydration disappeared and plasma sodium fell from 135 to 118 mEq /L After a few weeks however arterial pressure gradually fell to 120/70 mm Hg and the triple rhythm returned A slow infusion of 150 ml of NaCl 0 6 per cent did not raise the arterial pressure although it increased central venous pressure Plasma calcium was then found to be 2 3 mEq /L and the Q T time was prolonged With the administration of calcium lactate orally the plasma calcium rose in one week to 2 9 mEq /L and arterial pressure to 140/80 mm Hg the triple rhythm diminished but did not disappear and plasma sodium had come down to 112 mEq /L The patient was then given 44 mEq of calcium gluconate in 200 ml of 0 25 per cent glucose in the course of 92 minutes and the same effect was observed as in the first three observations (see Table I) It should be noted that, in this case potassium was within the normal range and did not change

The low concentration of sodium might have contributed to the development of hypotension as suggested by Merrill and associates[3] although in the in vitro experiments a low concentration of sodium appears to enhance rather than decrease the effect of calcium ions on the contraction force of the frog heart[22,24]

REFERENCES

1 Strawitz J G Howard J M and Artz C P Effect of i v calcium gluconate on post

Table I

	14 hr	*14 hr 45* *Start* (Ca gluconate infusion)	*16 hr 19* *End* (Ca gluconate infusion)	*18 hr*
Arterial pressure (mm Hg)	150/85	150/80	185/105	180/90
Triple rhythm	+	+	—	—
Q T time (sec)	0 38	0 36	0 28	
Normal range		0 27-0 36		
Ca		2 96	5 36	
Mg		1 58	1 44	
K (mEq /L plasma)		4 70	4 70	
Na		113	112	
HCO		22	22	
Inorganic phosphate (mg %)		10	10	
Venous pH		7 36	7 37	
Total protein (Gm /L)		56	55	

traction hypotension A.M.A. Arch. Surg. 70: 33, 1955.
2. Clowes, G. H. A., and Simeone, F. A.: Acute hypocalcemia in surgical patients. Ann. Surg. 146: 530, 1957.
3. Merrill, J. P., Levine, H. D., Sommerville, W., and Smith, S.: Clinical recognition and treatment of acute potassium intoxication. Ann. Int. Med. 33: 797, 1950.
4. Gorter, E., and de Graaff, W. C.: Klinische Diagnostiek. Leiden, 1955, Stenfert Kroese, p. 728.
5. Gornall, A. G., Bardawill, Ch. J., and David, M. M.: Determination of serum proteins by means of the biuret reaction. J. Biol. Chem. 177: 751, 1949.
6. Mijnoor, C. L. H.: The possibility of detecting individual proteins in blood serum by differentiation of solubility curves in concentrated sodium sulfite solution. Yale J. Biol. & Med. 18: 419, 1946.
7. Boen, S. T.: Peritoneal dialysis, M. D. thesis, Amsterdam, 1959, edited by Van Gorcum and Comp., Assen, Netherlands.
8. Kissin, M., Schwarzschild, M. M., and Bakst, H.: A nomogram for rate correction of the Q-T interval in the electrocardiogram. Am. Heart J. 35: 990, 1948.
9. Electrocardiographic Test Book, Vol. 1, American Heart Association, 1956, p. 156.
10. Ibid., p. 137.
11. McLean, F. C., and Hastings, A. B.: Clinical estimation and significance of calcium ion concentrations in the blood. Am. J. M. Sc. 189: 601, 1935.
12. Carter, E. P., and Andrus, F. C.: The Q-T interval in the human electrocardiogram in the absence of cardiac disease. J. A. M. A. 78: 1922, 1922.
13. White, P. D., and Mudd, S. G.: Observations on the effect of various factors on the duration of the electrical systole of the heart as indicated by the length of the Q-T interval of the electrocardiogram. J. Clin. Invest. 7: 387, 1929.
14. Balbo, M.: Parathyroidism. Ann. Surg. 96: 649, 1932.
15. Barker, P. S., Johnston, F. D., and Wilson, F. N.: The duration of systole in hypocalcemia. Am. Heart J. 14: 82, 1937.
16. Ernstene, A. C., and Proudfit, W. L.: Differentiation of the changes in the Q-T interval in hypocalcemia and hypopotassemia. Am. Heart J. 38: 260, 1949.
17. Surawicz, B. S., and Lepeschkin, E.: The electrocardiographic pattern of hypopotassemia with and without hypocalcemia. Circulation 8: 801, 1953.
18. Bellet, S.: The electrocardiogram in electrolyte imbalance. A.M.A. Arch. Int. Med. 96: 618, 1955.
19. Bechtel, J. T., White, J. E., and Estes, E. H., Jr.: The ECG effects of hypocalcemia induced in normal subjects with edathamil disodium. Circulation 13: 837, 1956.
20. Clark, A. J.: The action of ions and lipoids upon the frog heart. J. Physiol. 47: 66, 1913-14.
21. McLean, F. C., and Hastings, A. B.: A biological method for the estimation of calcium ion concentration. J. Biol. Chem. 107: 337, 1934.
22. Wilbrandt, W.: Zur Frage der Beziehungen zwischen Digitalis- und Kalziumwirkungen. Wien. med. Wchnschr. 108: 809, 1958.
23. Loewi, O.: Über den Zusammenhang zwischen Digitalis und Ca-wirkung. Arch. exper. Path. Pharmakol. 82: 130, 1918.
24. McGuigan, R. A., and Higgins, J. A.: The influence of Ca salts on digitalis action. J. Lab. & Clin. Med. 23: 839, 1938.
25. Danielopol, D., Draganesco, S., and Copaceanu, P.: Les sel de calcium dans l'angine tobe. Presse méd. 30: 413, 1922.
26. Loewenberg, L.: L'action cardiotonique et l'action diurétique du chlorure de calcium. Ann. méd. 13: 17, 1923.
27. Billigheimer, E.: Vergleichende Untersuchungen über die Wirkung und Wirkungsweise des Calciums und der Digitalis. Ztschr. klin. Med. 100: 411, 1924.
28. Bower, J. O., and Mengle, H. A. K.: The additive effect of Ca and digitalis. J.A.M.A. 106: 1151, 1936.
29. Nalbandian, R. M., Gordon, S., Campbell, R., and Kaufman, J.: A new quantitative digitalis tolerance test based upon the synergism of Ca and digitalis. Am. J. M. Sc. 233: 503, 1957.
30. Smith, P. R., Winkler, A. W., and Hoff, H. E.: Calcium and digitalis synergism. Arch. Int. Med. 64: 322, 1939.
31. Friedman, M., and Bine, R., Jr.: Observations concerning the influence of calcium upon the actions of digitalis glycoside. Am. Heart J. 36: 934, 1948.
32. Szent-Györgyi, A.: Advances in cardiology, Vol. 1, Basel, 1956, Karger.
33. Caviezel, R., Koller, M., and Wilbrandt, W.: Zur Frage der Kalium-Kalziumantagonismus am Herzmuskel und seine mögliche Beziehungen zum Ionentransporte. Helv. physiol. et pharmacol. acta 16: 72, 1958.
34. Niedergerke, R., and Lüttgau, H. C.: Calcium and contraction of the heart. Antagonism between calcium and sodium ions. Nature 179: 1066, 1957.

to distinguish these more fortunate persons from those who have a high expectation of death or disability from stroke or heart failure. For many years before effective hypotensive therapy was practicable we measured the basal blood pressure routinely by a standard technique.[3] The outlook for untreated patients appears to be related closely to the basal blood pressure and hardly related at all to the labile fraction of the blood pressure which we have called the supplemental blood pressure. Our practice has been to treat symptomless patients whose basal blood pressure was sufficiently high and in general to abstain from treating those whose basal blood pressure fell to a near normal level. In this connection it should be remembered that the normal range for basal blood pressures by the technique used is very much lower than for casual blood pressures. In general we consider that there is a strong indication to treat female patients whose basal blood pressure is in excess of 155/90 mm. Hg and males whose basal blood pressure is above 145/85 mm. Hg. Certainly in our follow-up study the mortality in untreated persons begins to rise more steeply after these levels.[24]

The follow-up of the first 8 years of our experience in treating Grade II hypertensive patients has yielded results which are now statistically significant. It appears that the mortality of Grade II patients who are on hypotensive therapy is approximately half that of corresponding Grade II patients or patients with slightly milder hypertension who have not had treatment ($p<0.001$).

The question whether something that might be described as preventive treatment should be administered is much in dispute. Our findings indicate clearly that of patients on treatment very few, if any, develop malignant hypertension. Furthermore, apart from patients who have advanced renal disease, very few develop congestive heart failure, and since 1953 the occurrence of strokes has diminished. The impression therefore is that such manifestations of hypertension are to some degree preventable. It is likely that the incidence of heart failure, stroke, and malignant hypertension can be diminished in patients with symptomless high blood pressure, and that therefore whenever the level of the blood pressure has risen to within the range at which such manifestations are likely to occur preventive therapy should be applied. Whether in those patients with very mild hypertension who have casual blood pressures in the region of 160/90 mm. Hg one should start by reducing the blood pressure is a matter concerning which there is legitimate ground for differences of opinion. My view would be that there is something to be said for maintaining such blood pressures in the fully normal range, provided that any drugs given do not produce side effects.

Preliminary approach to establishing a hypotensive regimen

Good reduction of blood pressure with few side effects depends upon adjusting the regimen to the responses of the individual patients. The procedures involved may be divided conveniently into preliminary measures by which the blood pressure is reduced, followed by a second stage in which adjustments are made to better the regimen by reducing side effects and effecting further improvements in the control over the levels of blood pressure. The initial approach will vary according to the urgency or mildness of the case, and whether the patient can be under all-day supervision during the induction of therapy. Most of our patients attend a day clinic where blood pressures may be measured throughout the day, and the effects of adjustments of dosage on the levels of blood pressure and the side effects are recorded.

One may divide drugs broadly into those suitable for background therapy, such as rauwolfia alkaloids and the hypotensive diuretics, and the more powerful drugs which may be described as the "gravity-augmented hypotensive drugs," which depend for their action on interference with homeostatic circulatory reflexes and which in consequence are associated with postural hypotension. There is no single ideal hypotensive drug, and in the majority of patients the most suitable therapy is by a combination of drugs.

Background therapy. There are some mild cases in which background therapy alone is sufficient to reduce the blood pressure to a satisfactory level, ideally to between 120/75 and 140/85 mm. Hg for as much of the

24 hour day as is practicable In mild cases therefore there is no objection to observing the effect of background therapy alone but in severe cases it is desirable to establish a good regimen as soon as practicable and one may start simultaneously with background therapy and one of the more powerful drugs the dose of the latter being increased by small amounts daily or even twice daily until the blood pressure begins to approach the desired level

Perhaps the most satisfactory single drug for background therapy at the present time is hydrochlorothiazide 50 mg night and morning with 5 grains of potassium chloride thrice daily Hydrochlorothiazide is preferable to chlorothiazide in that there are fewer side effects It has had a longer period of clinical trial than hydroflumethiazide which is approximately of equal potency A most interesting development is the drug chlormethiazide (Fluitran) which is at least ten times as potent as hydrochlorothiazide and may be used in doses as low as 2 to 4 mg twice daily Potassium chloride 1 Gm daily should be given with this drug at least until it is found whether such supplements are necessary

If only one drug were to be used for background therapy I should prefer a hypotensive diuretic to a rauwolfia alkaloid because even in doses which cause no mental depression rauwolfia alkaloids sometimes cause states of mental inertia and apathy and patients who make no specific complaint about side effects may feel better without them Such a statement does not apply to all or even a majority of patients Many take small doses of rauwolfia alkaloids 0 25 to 0 4 mg daily without side effects and with improvement in their mental as well as in their circulatory status It is difficult to decide in advance how a patient will react but we avoid rauwolfia alkaloids in patients at a time of emotional crisis or when there is a history of mental breakdown The use as a preliminary measure of 0 25 mg of reserpine daily in addition to hydrochlorothiazide is a suitable background therapy in a majority of patients and in a proportion of mild cases will be sufficient to reduce the blood pressure adequately There is usually no objection to the drugs being combined in one tablet. We found that 23 per cent of our patients could be controlled on background therapy alone but most of them were among the milder cases coming to us

Use of gravity-augmented hypotensive drugs There are now several chemical groupings of the drugs which by interfering with the action of the sympathetic nervous system prevent those homeostatic adjustments of the circulation which in hypertension are maintaining the level of the blood pressure at an abnormally high level It should be recognized that postural hypotension is not a side effect of these drugs but is an inevitable consequence of interfering with homeostasis In the case of the ganglion blocking drugs one may make the generalization that practically all stimuli which homeostatically call for increased activity of the sympathetic system lead to an increase of the hypotensive action of these drugs Probably this statement applies to all the gravity augmented hypotensive drugs because under such conditions the level of the blood pressure is more dependent on sympathetic vasoconstriction Conversely stimuli which call for a decrease in the homeostatic discharge of sympathetic impulses lead to a decrease in the response to gravity augmented hypotensive drugs because then the level of the blood pressure is less dependent on sympathetic vasoconstriction

There are many examples of the enhancement of the response to gravity augmented hypotensive drugs by procedures which are likely to call for increased homeostatic action by the sympathetic nervous system The effect of the gravity augmented hypotensive drugs is greatest when the patient is standing of intermediate degree when he is sitting and least when he is lying down The reason is that assumption of the vertical posture is compensated for homeostatically by an increased sympathetic discharge Restall and Smirk found that application of suction to the body surface has the same effect on the action of hexamethonium as does the vertical posture and for the same reason Venesection was shown by Freis and associates[77] and O Donnell[1 78] to enhance the response to hexamethonium Venous congestion of both lower limbs has the same effect The explanation is that bleeding or the pooling of blood in veins calls for

compensatory increase of the activity of the sympathetic nervous system hence there are more impulses to be removed by hypotensive drugs which act upon the homeostatic mechanisms Salt restriction was shown by Restall and Smirk[11] and Freis to increase the circulatory response to hexamethonium and this has been further confirmed by O Donnell[3] A decrease of plasma volume often occurs in patients deprived of salt and it seems likely that deprivation of salt leads to a homeostatic increase of the sympathetic activity The effect is not due solely to the depletion of sodium for O Donnell[24] showed that restoration of the blood volume in salt depleted patients by infusion of a salt free dextran solution reduced the postural hypotension induced by hexamethonium and abolished the enhancement of the action of hexamethonium by the salt deprivation Exercise by dilating blood vessels in the voluntary muscles meals by causing dilatation in the splanchnic system purgatives and diuretics by decreasing either the extracellular fluid volume or the plasma volume[21] would all appear to call for an increase in homeostatic activity of the sympathetic nervous system in order to prevent a fall of blood pressure and all may enhance the response to ganglion blocking drugs

There are also examples of a decrease of the response to ganglion blocking drugs which results from the application of procedures which are likely to call for decreased homeostatic action by the sympathetic nervous system Probably similar effects would be noted with all the gravity augmented hypotensive drugs Examples are the effect of immersion of the body in water[3] which acts by counteracting the effect of gravity upon the circulatory system administration of pressor drugs[11] such as noradrenaline angiotensin s methyl isothiourea and increase of blood volume by the infusion of blood or dextran solution[23]

If one of these potent drugs is required in order to reduce the blood pressure then to get the best effects with the smallest dose the patient should be standing or sitting during the day and during the night he should be propped up in bed with a back rest at an angle of 45 degrees In patients with severe hypertension the reduction of blood pressure during sleep alone is quite insufficient and also ineffective is the suggestion that the patient use an extra pillow We instruct our patients in the construction of a simple version of a cardiac bed (Smirk[4]) and the majority of our patients sleep sitting up

The gravity augmented hypotensive drugs may be divided into two main classes

1 Ganglion blocking drugs There are three chemical groupings of ganglion blocking drugs quaternary ammonium compounds such as pentolinium secondary amines such as mecamylamine and tertiary amines such as pempidine M & B 4500 and M & B 5409A All the ganglion blocking drugs inhibit the action of both the parasympathetic and the sympathetic nervous systems Hence some parasympatholytic side effects must be regarded as a usual association of the use of ganglion blocking drugs alone However if ganglion blocking drugs are used in combination with other drugs which potentiate the sympatholytic action the dose administered may fall below the threshold at which parasympatholytic side effects make their appearance Hexamethonium the first of these substances to be used in the treatment of hypertension is now almost superseded although on occasion for an investigation or to produce a prompt but comparatively brief effect injections of it are employed Oral hexamethonium is unsatisfactory for most patients because of unpredictable absorption and side effects

Pentolinium (Ansolysen)[14 11] was the next drug to be used widely and remains a valuable substance Over a period of 7 years extensive use long term toxic effects do not appear to have developed The substance may show unpredictable absorption but is satisfactory for many patients even more so since the effective dose can be reduced considerably when a background therapy of a rauwolfia alkaloid and a hypotensive diuretic is employed As with the use of most of the early quaternary ammonium compounds drug tolerance develops so that the dose has to be increased gradually for a period of perhaps 2 or even 3 months Eventually the dose becomes comparatively stable A suitable initial single dose is 20 mg but very large doses even 500 mg are required eventually in some patients

Chlorisondamine (Ecolid) resembles pentolinium closely. Its potency is approximately twice that of pentolinium. Trimethidinium (Ostensin) also resembles pentolinium closely,[17,18] but has the advantage that toleration to it does not occur to any appreciable extent. It is not completely absorbed from the alimentary canal and is a quaternary ammonium compound. Effective action seldom develops with less than 20 mg. (single dose) and doses of over 250 mg. are needed in some patients.

Mecamylamine (Mevasine, Inversine)[19] is a secondary amine and its principal difference from the quaternary ammonium compounds already mentioned is that it is absorbed completely from the alimentary tract and there is no appreciable development of drug toleration. If it is given on an empty stomach its absorption seems to be more predictable than that of any of the quaternary ammonium compounds. Unlike the quaternary ammonium compounds it has occasionally given rise to instances of long term toxicity. Gross tremors and severe mental disturbances, sometimes fatal, have occurred. When toxicity is recognized early the experience of our clinic has been that improvement occurs spontaneously on withdrawal of the drug. The dose of mecamylamine may be as small as 1.25 mg., which is a suitable initial dose, although most patients require more than 2.5 mg., and some require over 30 mg.

Pempidine (Perolysen) is a tertiary amine which, like mecamylamine, is completely absorbed from the alimentary canal. The action is more predictable than that of the quaternary ammonium compounds. Pempidine and its homologues, M & B 4500 and M & B 5409A, are at the present time the most potent of the ganglion blocking drugs.[20] They appear to be completely absorbed from the alimentary canal and do not lead to the development of drug toleration. No long term toxicity has emerged from their use. Pempidine is available in 1.5 and 10 mg. tablets. The initial dose of pempidine should be 1 or 2.5 mg., which may be administered before breakfast, at 2 P.M. and at bedtime. If the patient is well enough, the blood pressure should be taken while he is standing, since this will reveal the maximum extent of the fall of blood pressure. Attempts to bring the blood pressure down while the patient is lying down merely involves the use of much larger doses of ganglion blocking drugs with a corresponding increase of the side effects.

The dose may be raised rapidly. Our usual practice when blood pressures are being observed hourly or more frequently by trained technicians is to administer 2.5 mg. of pempidine initially and a further 1 mg. every hour and a quarter until the blood pressure has fallen to a perceptible degree, and then to continue administering the drug but at less frequent intervals until an effective dose has been discovered. In our experience the final dose attained has averaged 8.3 mg., and occasionally has been as high as 18 mg., but sometimes a dose of 2.5 mg. has been excessive and 1 mg. two or three times daily has proved sufficient with background therapy. If M & B 4500 is used, the doses are approximately half those of pempidine, whereas with M & B 5409A the dose is approximately 10 per cent higher than the dose of pempidine.

All of the ganglion blocking drugs can be used in virtually the same way, provided that they do not give rise to drug toleration. Mecamylamine (2.5 and 10 mg. tablets) may be used as an alternative to pempidine with 1.25 mg. as an initial dose, to be repeated at intervals of about one and a quarter hours until an effective dose has been discovered. The final dose varies greatly from patient to patient but is usually under 30 mg. and rarely as high as 70 mg. When patients are on background drugs the dosage range for mecamylamine is lower.

The sympatholytic drugs. Sympatholytic drugs without parasympatholytic effects of recent origin are bretylium tosylate (Darenthin), a quaternary ammonium compound, and guanethidine (Ismelin),[?] an amidine. Some obscurities remain as to their exact modes of action, but it is generally agreed that they affect the postganglionic part of the sympathetic nervous system in particular and probably have something to do with the release of noradrenaline at sympathetic nerve endings. In most patients either of these drugs in adequate dosage will reduce the blood pressure.

BRETYLIUM TOSYLATE (DARENTHIN). Although having a different site of

bretylium tosylate may be treated as if it were a ganglion blocking drug but without an effect upon the parasympathetic nervous system [41-43] It has the same order of duration of action as pempidine varying in individual patients from 3 to 12 hours larger doses produce a longer action [illegible]

Bretylium tosylate is not a highly potent drug and the large doses which have to be given when the drug is employed by itself may give rise to irregular action presumably because of irregular absorption We have encountered episodes of unexpectedly large variations of response in patients on large doses Although overactivity of the parasympathetic nervous system due presumably to some lack of balance resulting from depression of the sympathetic nervous system does not make itself evident in a majority of cases yet in some patients symptoms such as diarrhea and the exacerbation of dyspepsias suggest the occurrence of parasympathetic overactivity or preponderance Perhaps the large dose has something to do with the occurrence of indigestion

The effective single dose of bretylium tosylate will rarely be as low as 100 mg and may on occasion exceed 600 mg A single fully effective morning dose which reduces the trough blood pressure of the standing patient to about 130/85 mm Hg may cause a 12 hour reduction of blood pressure Usually we find that an additional somewhat smaller dose at about 2 P.M. is necessary for adequate control of the blood pressure.

GUANETHIDINE (ISMELIN) This drug has a much longer duration of action than does bretylium tosylate [43] Once the blood pressure has been brought down to a satisfactory level the return of the blood pressure to the original height after withdrawal of the drug may take 2 or even more days Hence with guanethidine care is needed to avoid cumulative effects A dose which may have little effect on the blood pressure on the first or second day may have an excessive action when continued We have preferred therefore to initiate guanethidine therapy gradually and have so far regarded it as less suitable than ganglion blocking drugs for starting treatment in severe cases The long duration of action has caused some apprehension lest a patient who might develop a cardiac infarction should be embarrassed by the long-continued action of the drug In several patients therefore I have used guanethidine in combination with background therapy and a small dose of a ganglion blocking drug so that in the event that discontinuance of hypotensive therapy became desirable a prompt decrease in the hypotensive action could be obtained by withdrawal of treatment

The administration of guanethidine has been associated on occasion with such side effects as muscle pains sensations of nervous tension nausea malaise nasal obstruction and failure of ejaculation as a rule without impotence Background therapy when used in combination with guanethidine may serve to eliminate any side effects which occur when the drug is given by itself Effective daily doses of guanethidine are usually less than 100 mg in divided doses and sometimes as low as 30 mg Even 180 mg daily may have no obvious effect on the blood pressure in the first few days but with accumulation may cause hypotension

Treatment by combination of drugs

Our general impression is that at the present time the best results are to be obtained by the use of suitable combinations of hypotensive agents In cases of milder hypertension the Grade II type of patients in whom there is no immediate urgency our recommendation would be to start with background therapy using 50 mg of hydrochlorothiazide at bedtime and breakfast time with 0.75 Gm of potassium chloride twice daily and 0.125 or even 0.25 mg of reserpine twice daily If the blood pressure is not unduly high it is practicable to wait 2 or 3 weeks for the action of the reserpine to become fully established If however the patient has a very high blood pressure for example a casual blood pressure of 230/130 mm Hg or higher it is usually desirable to add bretylium tosylate or guanethidine in gradually ascending doses If the patient can be observed continuously throughout the day our practice is to administer 100 mg of bretylium tosylate at intervals of approximately 1½ hours until such time as the blood pressure begins to fall This enables

one to judge the magnitude of an effective dose. The lowest dose we have used, combined with background therapy, is about 50 mg. thrice daily, before breakfast, at 2 P.M., and at bedtime. The highest dose of bretylium tosylate which we have used continuously is 600 mg. thrice daily. As a rule, however, if the requisite dose of bretylium tosylate has exceeded 300 mg., we have preferred to add small doses of one of the more potent ganglion blocking drugs, for example, pempidine, rather than increase further the dose of bretylium tosylate.

With a choice of many drugs which differ in their properties and have value in particular situations, the range of useful regimens cannot be briefly summarized. Among the ganglion blocking drugs, my first choice for administration to a previously untreated patient would be pempidine or one of its homologues, M & B 4500 or M & B 5409A.[44] Mecamylamine on occasion has given rise to gross tremors and to mental disturbance, with an occasional fatality, whereas the pempidine group of drugs does not appear to show delayed toxicity. If, however, a patient is already well controlled with some drug such as pentolinium, trimethidinium, or chlorisondamine, it will not need to be discontinued, but with these there is the disadvantage of drug toleration which, when therapy is initiated, will delay the establishment of a stable regimen. Patients who are on background therapy but who require the addition of a more potent substance will often remain comfortable when a ganglion blocking drug is added to the regimen. Alternatively, one may add bretylium tosylate or guanethidine, or a judicious combination of one of these with a ganglion blocking drug. By the selection of appropriate doses it is almost always practicable to avoid significant parasympathetic and parasympatholytic side effects.

It has been shown by Smirk[44] that with a satisfactory spacing of the drugs now available it usually happens that, if the blood pressure at the trough of the blood pressure fall is reduced to, or near to, a fully normal level of 120/80 mm. Hg, the blood pressure during the rest of the day is likely to be satisfactory. It was shown that the blood pressure at the trough of the blood pressure fall is closely related to the average pressure throughout the day.

Whenever all day tests are impracticable, the patient may be instructed to raise suitably spaced doses of the more potent hypotensive agents by small increments until such time as a slight faintness results at the trough of the blood pressure fall. The increments should be added at intervals of 1 or 2 days. If then the last small increment which gave rise to mild hypotension is removed, the probability is that an important degree of control of the blood pressure has been attained. Details of the method of establishing control by various ganglion blocking drugs has been published elsewhere. This method is applicable without modification to bretylium tosylate. In the case of guanethidine, however, adjustments in dosage must be gradual, and a week or more may elapse before the full effect of a change in dosage can be evaluated.

In severe cases, especially in patients with Grade IV retinal changes, troubles such as ileus are more likely to occur at an early stage if ganglion blocking drugs are used alone. To avoid this serious complication we give background therapy and replace some of the ganglion blocking drug with bretylium tosylate. Approximately equivalent doses are 4 mg. of pempidine equals 2 mg. of M & B 4500 equals 85 mg. of bretylium tosylate. Ileus or a threat of ileus seems to have been much less frequent since this practice was adopted.

Summary

1. At the present time very few patients should suffer persistent discomfort from the use of effective hypotensive therapy.

2. Although the hypotensive diuretics alone or even in combination with rauwolfia alkaloids will not always suffice to reduce the blood pressure much more than does a placebo, there is in almost every case a distinct enhancement of the response to ganglion blocking drugs and to the new sympatholytic drugs, bretylium tosylate and guanethidine. This action has a distinct advantage, for it makes possible a background form of therapy upon which comparatively small doses of ganglion blocking or sympatholytic drugs may suffice, even in severe cases.

3 For severe cases the most generally satisfactory approach is not by one of the sympatholytic drugs and background therapy alone but by the introduction additionally of a small dose of a ganglion blocking drug into the regimen in order to preserve a satisfactory balance between the activities of the sympathetic and parasympathetic nervous systems Even without background therapy it is usually possible to combine bretylium tosylate or guanethidine with a potent ganglion blocker in doses which give rise to no significant side effects from either group of drugs Background therapy is however desirable to obtain a more stable *regimen* If a sympatholytic drug is to be combined with a ganglion blocking drug it is preferable to use a ganglion blocking drug to which there is not significant toleration Mecamylamine and pempidine with its potent homologues M & B 4500 and M & B 5409A are examples In patients who have had a peptic ulcer it seems unwise to use sympatholytic drugs without employing ganglion blocking drugs to restrain gastric secretion

REFERENCES

1 Smirk F H Methonium compounds in hypertension Lancet 2 477 1950
2 Smirk F H Blood pressure reduction to selected level by continuous injection of methonium halides (C5 and C6) and the use of an electrically operated syringe Am Heart J 42 30 19 1
3 Smirk F H *Pathogenesis of essential hypertension* Brit M J 1 791 1949
4 Smirk F H High arterial pressure Oxford 19 7 Blackwell Scientific Publications p 683
5 Ferry H M Effect of blood pressure reduction on prognosis in hypertension *I* Hypertension edited by J H Moyer Philadelphia 1959 W B Saunders Company p 115
6 Barnett A J Ocular effects of methonium compound *Brit J Ophthal 36 593 1952*
7 Campbell A J M Graham J G and Maxwell R D H Treatment of hypertension by oral methonium compound Brit M J 1 251 1952
8 Ford R V and Spurr C L The treatment of the ambulatory hypertensive patient with hexamethonium administered orally Am Pract & Digest Treat 5 251 1954
9 Morrison B Parenteral hexamethonium in hypertension Brit M J 1 1291 1953
10 Murphy E A Treatment of hypertension with hexamethonium bromide Lancet 2 899 1951
11 Platt R Hypertensive retinopathy and its medical treatment Quart J Med n s 23 441 1954
12 Rosenheim M L Discussion on the medical treatment of hypertension Proc Roy Soc Med 45 269 1952
13 Smirk F H and Alstad K S Treatment of arterial hypertension by penta and hexamethonium salts Brit M J 1 1217 1951
14 Campbell A and Robertson E Treatment of severe hypertension with hexamethonium bromide Brit M J 2 804 1950
15 Harington M and Rosenheim M L Hexamethonium in the treatment of hypertension Lancet 1 7 1954
16 Kelley R T Freis E D and Higgins T F The effects of hexamethonium on certain manifestations of congestive heart failure Circulation 7 169 1953
17 Palmer A J The management of hypertension with hexamethonium bromide M J Australia 2 428 1952
18 Smirk F H Practical details of the treatment of hypertension by hexamethonium salts and by pentamethylene 1 5 bis (methyl pyrrolidinium) bitartrate (M & B 2050) New Zealand M J 52 325 1953
19 Smith K S and Fowler P B S Prevention and treatment of hypertensive heart failure by ganglion blocking agents Lancet 1 417 1955
20 Smirk F H Hamilton M Doyle A E and McQueen E G The treatment of hypertensive heart failure and of hypertensive cardiac overload by blood pressure reduction Am J Cardiol 1 143 1958
21 Doyle A E Electrocardiographic changes in hypertension treated by methonium compounds Am Heart J 45 363 1953
22 Hay D R Electrocardiographic changes in treated hypertension Australasian Ann Med 6 311 1957
23 Smirk F H Casual and basal blood pressures IV Their relationship to the supplemental pressure with a note on statistical implications Brit Heart J 6 176 1944
24 Smirk F H Veale A M O and Alstad K Basal and supplemental blood pressures in relationship to life expectancy and hypertension symptomatology New Zealand M J 58 711 1959
25 Smirk F H McQueen E G and Morrison R B I Chlorothiazide and hydrochlorothiazide in the management of hypertension Brit M J 1 515 1960
26 Kestall P A and Smirk F H Regulation of blood pressure levels by hexamethonium bromide and mechanical devices Brit Heart J 14 1 1952
27 Freis E D Stanton J R Finnerty F A J Schnaper H W Johnson R L Rath C E and Wilkins R W The collapse produced by venous congestion of the extremities or by venesection produced by venous congestion of the extremities or by venesection following certain hypotensive agents J Clin Invest 30 435 19 1
28 O Donnell T V Variations in postural hypotension with changes in blood volume Proc Univ Otago Med Sch 33 29 1955
29 O Donnell T V Studies postural hypoten

sion following ganglion blocking drugs Clin Sc 18 237 1959

30 Restall P A and Smirk F H The treatment of high blood pressure with hexamethonium iodide New Zealand M J 49 206 1950

31 McQueen E G and Morrison R B I The hypotensive action of diuretic agents Lancet 1 1209 1960

32 Restall P A and Smirk F H Regulation of blood pressure level by hexamethonium bromide and mechanical devices Brit Heart J 14 1 1952

33 Doyle A E and Smirk F H The neurogenic component in hypertension Circulation 12 543 1955

34 Smirk F H Effects of hexamethonium bromide homologues Proc Univ Otago Med Sch 30 13 1952

35 Smirk F H Action of new methonium compound in arterial hypertension Lancet 1 457 1953

36 Maxwell R D H and Campbell A J M New sympathicolytic agents Lancet 1 455 1953

37 Kuhns K Liebeskind H and Muller W Zur Behandlung der Hochdruckkrankheit mit Ganglienblockern klinische Prüfung einer neuen bisquaternaren Verbindung (Ha 106) Ärztl Wchnschr 11 1053 1956

38 Smirk F H Ganglionic blockade by trimethidinium methosulphate Am Heart J 58 01 1959

39 Freis E D and Wilson I M Mecamylamine a new orally effective hypotensive agent A M A Arch Int Med 97 551 1956

40 Smirk F H and Hodge J V Six new hypotensive chemical relatives of pempidine J Clin Pharmacol & Therap (In press)

41 Boura A L A Green A F McCoubrey A Laurence D R Moulton R and Rosenheim M L Darenthin hypotensive agent of new type Lancet 2 17 1959

42 Smirk F H and Hodge J V Hypotensive action of bretylium tosylate Lancet 2 673 1959

43 Page I H and Dustan H P A new potent antihypertensive drug J A M A 170 1265 1959

44 Smirk F H Relationship between the trough blood pressure and the mean daily blood pressure in the course of ganglionic blockade New Zealand M J 14 527 1959

Annotations

The blight of medical science

Allan Gregg once said "The medical literature of today exemplifies all too fully the biological adage that life is choked by its own secretions." It is clear that the ever increasing volume of scientific medical production in this country primed fostered forced and bought by millions of dollars lavished on institutions and individual careers within itself the lethal seed of oblivion. To be of permanent value research need to record publish and publicize its results. Yet the tidal wave of overproduction in the biological sciences has made it almost impossible (a) to provide forums for early presentation in the conventional framework of scientific journals and (b) for the individual investigator to know and assess the activities of others even in his own limited field. I address before the Southern Society for Clinical Research A. Segaloff[1] has raised this problem. According to Segaloff today 25 000 journals are devoted to the biological sciences containing in a single year some two million articles on biology. It is interesting that this appalling state seemed to have alarmed very few scientists yet obviously it is of immediate and worldwide concern. Some time ago during "Symposium on Utilization of Recorded Knowledge"[2] G. M. Conrad demonstrated the nearly parabolic curve of journal growth in the field of biology which showed that even present methods of abstracting will become totally inadequate during the present decade. This means that the more investigations have been completed the less the likelihood that anyone will know about it. Into this climate comes the estimate of the Bayne Jones report on "The Advancement of Medical Research and Education." The report, plea for more and better medical training areas states that 20 000 new medical scientists (conservatively 0 000 additional papers per year) will be added to the load by 1970 in this country alone. A more recent analysis[3] stresses the need for the immediate creation of at least 20 new medical schools in this country. If this is realized and if present standards prevail, a sharp increase in the output of medical research far beyond the present anticipated increase in volume can be predicted. Private abstracting services the always incomplete abstract sections of some journals Biologic Abstracts in the U.S. (56 000 per year) Chemical Abstracts, or similar services in the U.S.S.R. (106 000 articles per year) are already inadequate. Mere indexing alone does not suffice. Segaloff suggests that most journals should only publish abstracts prepared by the author himself who would also be required to code his results according to a universal system. A central institute could microfilm and distribute the original manuscript on request. The machine code identical for any language would thus become the universal language of science.

This seems radical but it is likely that publication of full articles other than reviews will become an anachronism whether we like it or not. Few of us read a journal or even an article from beginning to end but rely on carefully written introductions (to discover the problem) and summaries (to know what was done and what was accomplished). "Federation abstracts" for example abstracts of the annual meetings of the Society for Clinical Investigation (June issues of *Journal of Clinical Investigation*) and similar services (Clinical Research and others) are often sufficiently detailed.

a first approximation even for those working in the field. It might be argued. Why waste excessive printing cost and time if the essential information can be obtained from carefully written abstracts. If such a radical departure in methods of communication in science becomes necessary and it seems that something must "give" soon several copies of full manuscript, tables and illustrations intended for publication in a national journal should be submitted to the editor and his editorial board for review before even an abstract of the manuscript is accepted for publication. Reprints of the abstract must be made available. The full text of the communication should be deposited in several regional centers where the article could be studied in the original or where competent staff could supply microfilm copies and translations on demand. The libraries of many medical centers may serve as a nucleus for such information centers. The considerable expenses involved must in a large measure be charged to research and agencies granting funds for research must then include in their appropriations large sums for financial support of a communication system of some sort, a suggestion recently made by Milton Lee and incorporated in the report mentioned above. Thus two kinds of journals can be visualized the abstract journal which is primarily directed to the medical research worker and the review journal such as *Medicine* or *Physiologic Reviews* which are designed exclusively as projects in postgraduate education. To be truly effective such changes would require the cooperation of all national biological groups editors of clinical and preclinical journals library associations and national health agencies. It needs international acceptance as well possibly through the UNESCO and the World Health Organization.

Although the medical scientist and the ultimate consumer the practicing physician are only dimly aware of the problem strong efforts are being made to stem the tide before it becomes unmanageable An increasing number of medical information centers have been created in this country such a the National Library of Medicine The National Science Foundation The National Academy of Science and others which provide such services as part of their activities In specific areas there exists cardiovascular research project (NHI) cancer chemotherapy information center (NIH) and a psychopharmacology service information center The over-all training and developmental research in the area of scientific communication is planned and carried out by newly founded Institute for Advancement of Medical Communication As an experimental example this Institute assisted in UNIVAC programming of the 1960 meetings of the Federated Societies of Biology and Medicine An International Conference on Scientific Information was held in Washington in 1958 and has issued its voluminous Proceedings by itself perhaps proof of the inadequacy of our present communication system A Conference of Biologic Editors (CBE) has been formed whose committees are concerned with many of the pressing facts of medical communication In consultation with other groups such as the American Medical Writers Association CBE is about to publish Style Manual as a first step toward unifying certain obvious aspects of medical writing and editing practices

We are likely to see significant changes in medical communication in our time Medical scientists and clinical investigators will have to recognize their responsibilities in this respect Little can be accomplished however if a well written abstract does not count if the practice of a forced completed manuscript is tied to an oral presentation before a clinical society or if scientific groups and universities continue to gauge an investigator qualification by the number rather than the substance of his publication This fosters quantitative mediocrity one of the major contributors to the blight of medical science

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REFERENCES

1 Gregg A Language and the practice of medicine The Diplomate 15 115 1943
2 Segaloff A Communication as a problem of science Clin Res 315 1959
3 Conrad G M Growth of biological literature and the future of biological abstracts Fed Proc 16 711 1957
4 Bayne-Jones S Chairman Consultants on Medical Research and Education The Advancement of Medical Research and Education Special Report Department of Health Education and Welfare U S Government Printing Office June 7 1958
5 Bayne-Jones S Chairman Committee on Consultants in Medical Research (Subcommittee of Departments of Labor and Health Education and Welfare) Committee on Appropriations U S Senate 86th Congress Federal Support of Medical Research
6 Lee M Proceedings of the International Conference on Scientific Information Area 7 1959 p 7
7 Orr R H An integrated approach to documentation Am Documentation 10 214 1959
8 Orr R H Proceedings of the International Conference on Scientific Information Washington D C 1959 National Academy of Science
9 Orr R H The CBE style manual for biological journals a progress report Mississippi Valley M J 82 1960

Bruit de Roger

If a harsh murmur with or without an accompanying thrill is found to be most intense just to the left of the sternum in the third or fourth intercostal space the differential diagnosis revolves about interventricular septal defect and isolated pulmonic stenosis The latter condition was less well defined in Roger time In favor of septal defect is left as well as right ventricular enlargement as determined by x-ray examination or fluoroscopy as well as by electrocardiography Bundle branch block is helpful if present and prominent pulmonary vascular markings with or without hilar pulsations are characteristic In pulmonic stenosis there is right ventricular enlargement only and the vascular markings are less well defined although poststenotic dilatation may produce prominent left hilar shadow Transmission of the murmur to the right in septal defect and upward and to the left in pulmonic stenosis is rarely of much help in differentiating the two conditions clinically

Interauricular septal defect can sometimes be confusing here since the lesion may produce a murmur in the same region although associated thrill is uncommon The murmur is believed to arise in the pulmonary artery because of the turbulence caused by increased *pulmonary blood flow* The prominence of the pulmonary artery in both hila as well as the hilar dance are usually distinguishing features but differentiation from interventricular septal defect is not always possible *Today* these clinical surmises can be confirmed or denied by the catheter and in the operating room

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Concept of a dual circulation

In recent years the argument that some of the blood flowing through the skin is not involved in the nourishment of the tissue has become universally accepted. Arteriovenous shunts have been demonstrated histologically and much information has been gathered about their regulation and their role in the control of the temperature of the body. Analogous shunts in skeletal muscle are vigorously denied since only a few morphologic demonstrations of such vessels have been reported and almost all of the evidence for shunts in muscle is inferential. The weight of these circumstantial demonstrations, however, is increased by their consistency and the number of experiments which cannot be easily explained in any alternative fashion.

One difficulty in accepting the concept of vascular shunts in muscle has to do with assigning to them a valid physiologic role. Although the movement of large volume of blood through the skin serves to regulate the temperature of the body, movement of blood through skeletal muscle can have no similar effect. The participation of an increase in the flow of blood through muscle in regulation of the blood pressure is hardly more likely since many alternative tissues are available through which compensatory increases in the flow of blood can easily be achieved. As a third alternative we suggest that the blood flowing through the shunts brings to the muscle a quantity of heat which causes an increase in temperature that might increase efficiency of contraction. Although the amount of heat which could be carried by such a system would be small in comparison to that locally produced during contraction of the muscle, such a mechanism could prepare for the initial response.

It is interesting to note that the shunt circulation in this tissue is undoubtedly under central nervous control. Vasodilator fibers have been demonstrated to be supplying muscles in animal preparations in which these phenomena have been studied. These fibers arising in the central nervous system may be associated with the motor outflow to skeletal muscle and thus might serve to increase the flow of blood in those specific muscles which are soon to be activated.

Such a shunt circulation would have interesting clinical implications. It would help to explain those paradoxical situations in which the total flow of blood through a muscle is increased yet the underlying pathologic complaint, viz. claudication or inadequate tissue nutrition, still persists.[7] Obviously, agents or mechanisms which open the shunt circulation without modifying nutritional supply would contribute to an increased total flow of blood but would in no way increase the turnover of tissue solutes and hence would not obviate the basic malnutrition of this tissue.

Much work remains to be done on this problem since the existence of a shunt circulation in the muscles of human beings has not yet been clearly demonstrated and since actual control of the vessels is uncertain in all but a very few species. The explanation or rather rationalization for the function of such bypass systems is highly conjectural and waits further experimental study.

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REFERENCES

1. Clara, M.: Die Arterio-venosen Anastomosen: Anatomie, Biologie und Pathologie, Leipzig, 1939, Barth.
2. Griffin, C. J.: Alternate circulatory routes in human skeletal muscle, M. J. Australia 2:859, 1959.
3. Hyman, C.: Physiological implications of a dual circulation in muscle, Angiologie 9:25, 1957.
4. Sheard, C.: Temperature of skin and thermal regulation of the body, *In* Otto Glasser, editor: Medical Physics, Vol. I, Chicago, 1947, Year Book Publishers, Inc.
5. Roddie, I., and Shepherd, J. T.: The effect of carotid artery compression in man with special reference to changes in vascular resistance in limbs, J. Physiol. 139:377, 1957.
6. Uvnäs, B.: Sympathetic vasodilator system and blood flow, Physiol. Rev. (Suppl. 4) 40:69, 1960.
7. Hyman, C., Rosell, S., Rosen, A., Sonnenschein, R. R., and Uvnäs, B.: Effects of alterations of total muscular blood flow on local tissue clearance of radio-iodide in the cat, Acta physiol. scandinav. 46:358, 1959.
8. Hyman, C., and Winsor, T.: Blood flow redistribution in the human extremity, Am. J. Cardiol. 4:566, 1959.

Cardiac glycosides and the kidney

Withering was certainly aware of the cardiac action of digitalis but attributed the clinical improvement that followed its administration to patients with dropsy to an increased excretion of urine as a result of a primary direct effect on the kidneys. Subsequently, many clinical and experimental observations in patients with congestive heart failure have established that the cardiac glycosides initially effect

an improvement in myocardial function and circulatory dynamics. With this in mind it was held that the observed diuresis was related to the accompanying increase in glomerular filtration rate and renal blood flow. This concept was supported by the observations of Bartram[1] who was unable to show clear-cut unilateral diuresis in response to the intrarenal arterial injection of Digitan. In contrast, Farber and associates[2] noted that in a few edematous subjects the intravenous administration of digoxin was followed by a slight diuresis and natriuresis without any prior or accompanying hemodynamic changes. Following the observations by Schatzmann[3] on the influence of the cardiac glycosides on the rate of transport of sodium and potassium across the membrane of the human erythrocyte, a number of investigators have shown that these agents reduce alterations in the bidirectional flux of several ions across the membranes of many other cells.

A direct renal response evoked by cardiac glycosides or aglycones has been confirmed by recent reports from several laboratories,[4-7] including our own, in which simultaneously comparative analyses of the function of both kidneys have been made after the slow unilateral renal arterial injection of these agents. In our experimental preparations the effects include a striking increase in the rate of flow of urine from the ipsilateral kidney amounting to 3 to 4 times the rate from the contralateral kidney. Along with this diuresis there is natriuresis and a chloruresis. Changes in the rate of excretion of potassium are variable and of small degree. A pronounced ipsilateral increase occurs in the excretion of calcium and to a somewhat lesser extent of magnesium as well. Both the glomerular filtration rate and renal plasma flow of the ipsilateral kidney decline initially but return toward control level thereafter.

It appears more and more likely that the primary change in cardiac function which is responsible for the observed beneficial therapeutic effects of the cardiac glycosides in patients with congestive heart failure is induced by the alterations in the rate of movement of ions across the myocardial cell membrane. The observations cited above lead to the conclusion that these drugs also directly affect active renal tubular transport mechanisms for several ions in a manner which promotes diuresis. Much work remains to be done to elucidate further the intriguing effects on the interrelated patterns of excretion of electrolytes and water induced by these drugs and the manner in which their activity is seemingly enhanced or inhibited by altered distribution of electrolytes.

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REFERENCES

1. Bartram, E. A.: Experimental observations on the effect of various diuretics when injected directly into one renal artery of dog, J. Clin. Invest. 11:1197, 1932.
2. Farber, S. J., Alexander, J. D., Pellegrino, E. D., and Earle, D. P.: Effect of intravenously administered digoxin on water and electrolyte excretion and on renal functions, Circulation 4:378, 1951.
3. Schatzmann, H. J.: Herzglykoside als Hemmstoffe für den aktiven Kalium- und Natriumtransport durch die Erythrocytenmembran, Helvet. physiol. et pharmacol. acta 11:346, 1953.
4. Hyman, A. L., Jaques, W. E., and Hyman, E. S.: Observations on the direct effect of digoxin on renal excretion of sodium and water, Am. Heart J. 52:592, 1956.
5. Koch, A.: Effect of ouabain on renal electrolyte transport in anesthetized dogs, Physiologist 1:47, 1958.
6. Cade, J. R., Shalhoub, R. J., and Canessa, M. L.: Effect of strophanthidin on transport mechanisms of the renal tubule, Fed. Proc. 19:370, 1960.
7. Kupfer, S., and Kosovsky, J. D.: Alterations in renal hemodynamics and tubular function following the intrarenal arterial injection of digitalis glycosides, Clin. Res. 8:186, 1960.

Book reviews

THE HEART IN INDUSTRY Edited by Leon J Warshaw M D F A C P Consultant in Occupational Health Medical Director Paramount Pictures Corporation Medical Director United Artists Corporation New York New York 1960 Paul B Hoeber Inc 677 pages Price $16

The Editor opening chapter a particularly well written survey of cardiovascular disease in industry sets the scene for the chapters which follow These present in comprehensive yet understandable form present-day concepts of the effect of heart disease on the patient and his ability to work the effects of work on the course of his heart disease and certain problems presented by the cardiac worker to his employer Along with the conventional subjects expected in such volume there are noteworthy presentations on the cardiac as vehicle operator in transportation the cardiac on the farm (a particularly refreshing sequence from the Purdue Farm Cardiac Project—incidentally neither author is a physician) cardiovascular effects of toxic occupational exposures (including a discourse on fundamental toxicology) traumatic heart disease (a subject often overlooked by nonsurgical practitioners of cardiology) and health education in industry (wherein the approach to the individual receives proper emphasis) Although most topics are well handled the treatment of workmen compensation and heart disease misses the mark As perceived by this reviewer this chapter attempts a description of the evolution of workmen compensation doctrine followed by an apology for the inconsistent unscientific decisions so prevalent today with implied criticism of some of the current efforts to achieve a sounder medicolegal operation in this chaotic field

Considerable repetition of content is present In fact one wonders about such consistency in point of view on the part of the different authors in introducing and developing their topics Does this reflect the guiding hand of the Editor is it provincialism (the majority of the collaborators are New Yorkers) or does a state of general agreement actually exist about matters relating to work and heart disease? At any rate the prevailing concepts are both reasonable and constructive

The format of the book and the relatively uncomplicated presentation of such matter make easy reading Typographic errors detected by the reviewer were infrequent especially for a first printing Numerous tables lend clarity to the material presented The lists of references at the end of each chapter although limited serve to introduce the interested reader to some key publications on each subject

Intended for both the industrial physician and the private practitioner written by clinicians for clinicians emphasizing the practical rather than the theoretical —these are among the attributes of the book listed by the Editor and publishers It does indeed well fulfill these characteristics and should be widely read

HYPERTENSION VOLUME III RENAL ELECTROLYTE AND AUTONOMIC FACTORS (Proceedings of the Council for High Blood Pressure Research, American Heart Association November 1959) Edited by Floyd R Skelton (MD, Ph D Research Director The Urban Maes Research Foundation and Associate Professor of Pathology Louisiana State University School of Medicine New Orleans La) New York 1960 American Heart Association 150 pages

This publication represents the Proceedings of the Council for High Blood Pressure Research of the American Heart Association November 1959 Six papers are presented The first paper is by Dr Louis Tobian on The Juxtaglomerular Apparatus in Experimental Hypertension in which considerable circumstantial evidence relating the granularity of juxtaglomerular apparatus of Goormaghtigh to renin secretion is cited A second paper by E E Muirhead presents evidence that the renal medulla may be the critical portion of the kidney which protects against renoprival hypertension A third paper by *O M Helmer and W E Judson* describes the isolation of vasopressor material from the renal vein of some but not all hypertensive subjects as well as of normotensive subjects with congestive heart failure

In fourth paper by S M Friedman and co workers evidence is presented which suggests relationship between contraction of smooth muscle and the gradient between intracellular and extracellular sodium A fifth paper by Dr F J Haddy discusses the function of small and large peripheral vessel The importance of oppositely directed changes in arteriolar and venular resistance are stressed and possible reflex arteriolar constriction secondary to venous hypertension is noted The final paper by S J Sarnoff and co-workers is entitled The Regulation of Function in the Innervated Heart In a series of elegantly contrived and painstakingly executed experiments the authors demonstrate that sympathetic and vagal stimulation do *not* primarily alter distensibility characteristics of the heart muscle but exert their effect on contractility These observations serve to support Starling concept that neural and chemical factors can serve to increase or decrease the contractile response of heart muscle to a given stretch

The various approaches to problems relating to the circulation and hypertension are presented in some detail and amplified and clarified by the group discussions which follow

American Heart Journal

March 1961 Volume 61 Number 3

Editorial

Earlier dialysis and anabolic steroids in acute renal failure

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Leeds, England

Acute reversible renal failure (often termed "acute tubular necrosis") is met with in many branches of medical practice. Of those patients referred to Leeds for treatment with the artificial kidney approximately 50 per cent can be classified as surgical or traumatic, 30 per cent as medical, and 20 per cent as obstetric cases. Now that artificial kidney units are commonplace, there has been a rapid development of understanding of the uses and limitations of these machines, and this has increased rather than diminished the need for rational therapy in patients with this syndrome. The symptoms of uremia are due to the accumulation of the products of tissue breakdown, and treatment should therefore be directed to (1) the removal of these products by dialysis and (2) the reduction of protein catabolism. In recent years there has been both a reappraisal of the time for dialysis in order to control the uremia more effectively and also of the methods available to reduce protein catabolism.

The trend at present is toward earlier and more frequent dialysis.[1,2] This is unnecessary in those patients with acute tubular necrosis who have a rate of rise in blood urea nitrogen of less than 30 mg. per cent per day. In these patients with adequate treatment, including the use of the artificial kidney when necessary either on clinical grounds or when the blood urea nitrogen reaches 200 mg. per cent, the recovery rate is more than 90 per cent.

In regard to patients with a high rate of protein catabolism, in whom the blood urea nitrogen rises more than 30 mg. per cent per day, the results are far less satisfactory, and on the basis of the above-mentioned criteria for dialysis, recovery occurs in only about 30 per cent of patients. Acute renal failure in this group of patients is almost always a complication of surgical or accidental trauma, and similar low rates of recovery have been reported in other series among patients with traumatic renal failure. The main cause of mortality in these patients is either the primary lesion (especially in the accidental trauma group) or complications related to the uremic state, particularly infection, and these are the patients in whom the use of earlier dialysis results in improved survival rates. Daily dialysis[1] and continuous dialysis require a great deal of equipment and staff, besides being more troublesome for the patient, and it has been shown that in this group of patients

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Book reviews

The Heart in Industry. Edited by Leon J. Warshaw, M.D., F.A.C.P., Consultant, Occupational Health; Medical Director, Loew's Theatres Corp.; Medical Director, United Artists Corporation, New York. New York, 1960. Paul B. Hoeber, Inc. 672 pages. Price $16.

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Hypertension. Volume III. Renal, Electrolyte and Neurogenic Factors (Proceedings of the Council for High Blood Pressure Research, American Heart Association, November 1959). Edited by Floyd R. Skelton, M.D., Ph.D., Research Director, The ... Mary Reese ... Foundation ... Professor of Pathology, Louisiana State University School of Medicine, New Orleans, La. New York, 1960. American Heart Association. 150 pages.

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The various approaches to problems relating to the circulation and hypertension are presented in some detail and amplified and clarified by the group discussions which follow.

various reasons perhaps because the anabolic steroid is incapable either of preventing breakdown of devitalized tissue or of accelerating anabolism of nitrogenous material other than that produced from normal cells Another possibility is that these patients are under considerable stress and may well produce a large quantity of adrenal cortical hormones which are known to be catabolic and have been shown experimentally to antagonize the effects of synthetic anabolic steroids[?] The patients in whom anabolic steroids are of negligible value are in fact usually those in whom acute renal failure follows surgical or accidental trauma and these are the patients in whom earlier dialysis is of such importance in reducing the mortality rate

At the start of the recovery phase from acute renal failure patients are often malnourished and this renders them particularly liable to infection poor healing of wounds and prolonged and difficult convalescence It has been shown that patients treated with anabolic steroids during the uremic phase of their illness returned to nitrogen equilibrium far quicker than did corresponding patients who had been treated with glucose alone [?]

The way in which the so called anabolic steroids act is so far unknown It is uncertain whether they are in fact anabolic or whether they may be anticatabolic in action or perhaps both In patients with acute renal failure after pregnancy the action does not seem to be related to androgenicity because testosterone is much less effective than norethandrolone in these patients[?] Unfortunately similar experiments have not yet been carried out on patients with acute renal failure from other causes and in particular in male patients Neither is the action of these steroids related directly to their progestational properties for although progesterone has been shown to be anabolic in two patients with acute renal failure after pregnancy[?] progesterone and related steroids with a β orientated side chain at C_{17} are usually catabolic[?] It is possible that the greater effectiveness of norethandrolone in patients with acute renal failure after obstetric accidents may be due to its progestational activity but nandrolone phenyl propionate which has no progestational activity is probably as effective as norethandrolone in patients other than those with acute renal failure after pregnancy

Anabolic steroids have a relatively rapid action on protein catabolism the full effect is seen within 24 hours after administration is started[?]

The side effects of treatment with anabolic steroids include virilization and the development of jaundice but since treatment for acute renal failure is for only a short time these are unlikely to be of significance We have seen transient hypercalcemia in one patient who had traumatic uremia with multiple fractures while being treated with norethandrolone during the early recovery phase This may resemble the hypercalcemic syndrome with nephrocalcinosis which has been reported in patients who had osteolytic bone lesions and were immobilized while receiving androgens and estrogens[?]

The use of anabolic steroids in acute reversible renal failure can be justified on three grounds

1 If by their use the rate of protein breakdown can be reduced so that the rate of rise in blood urea nitrogen is less than 30 mg per cent per day it is probably necessary generally to dialyze these patients only when signs of clinical deterioration begin to appear and more cases can be managed without the need for dialysis Even if this is not possible if the rate of protein breakdown can be slowed at all fewer dialyses will be required so that fewer blood vessels need be sacrificed and more time will be available for mobility physiotherapy investigations and any other necessary treatment

2 It seems probable that the effect of calories in depressing protein breakdown is relatively insignificant in comparison with the effect of anabolic steroids Because many patients find the toleration of hypertonic glucose by mouth difficult it would appear that if such patients are given anabolic steroids the glucose could be replaced by more palatable fluids It may even be possible to give patients protein[?] possibly in the form of milk or synthetic amino acids in order to assist protein anabolism Animal experiments have suggested that l lysine may be useful[?]

3 There is no doubt that during three

or four weeks of oliguria on a low protein diet these patients suffer from progressive and extreme starvation. Undoubtedly this must contribute to the mortality and morbidity which occur during the recovery phase from acute renal failure. Therefore any treatment which conserves body protein will be of value in preventing the occurrence of late complications while also shortening the period of convalescence which these patients require.

In light of the foregoing, it would seem reasonable to use the newer anabolic steroids routinely in the management of all patients suffering from acute reversible renal failure.

REFERENCES

1. Sal tors I F Timely ... delayed ... the ... kidney. Arch. Int. Med. 101: ... 1958.
2. Teschan P. E., O'Brien T. F., and Baxter C. R.: Prophylactic ... haemodialysis in the treatment of ... renal failure. Clin. ... 40 1959.
3. Scribner B. H., ... J. I. ... haemodialysis in human ... Clin. Res. ... 8 1... 1960.
4. Scribner B. H., Magrid C. J., and Burnell J. M.: ... dialysis in the management of acute renal failure. Clin. Res. Pr. 8 136 1960.
5. Parsons F. M., Hobson S. M., Blagg C. R., and McCracken B. H.: Optimum time for dialysis in acute reversible renal failure: description and value of an improved dialyser with large surface area. Lancet 1:129 1961.
6. Parsons F. M., and McCracken B. H.: The artificial kidney. Brit. M. J. 1: 740 1959.
7. Kl... J. ... S. J. ... and Beebe R. T.: Acute renal failure. New England J. Med. 262 481 1960.
8. Sh...km ... P., Milne M. D., and Struthers N. W.: Oliguric renal failure of surgical origin. Brit. M. J. 2 14... 1960.
9. Bluemle L. W., Jr., Webster G. D., Jr., and Elkinton J. R.: Acute tubular necrosis. Arch. Int. Med. 104 180 1959.
10. Smith L. H., Post R. S., Teschan P. E., Abernathy R. S., Davis J. H., Gray D. M., Howard J. M., Johnson K. E., Klopp E., Mundy R. L., O'Meara M. P., and Rush B. F.: Post traumatic renal insufficiency in military casualties. II. Management, use of an artificial kidney, prognosis. Am. J. Med. 18 187 1955.
11. Borst J. G. G.: Protein katabolism in uraemia. Lancet 1 8... 1948.
12. B... G. M., Jockes A. M., and Lowe K. C.: Comments on the treatment of ... uraemia. Lancet 2: ...79 1949.
13. Ma...son C. M. C., Correia A. C., and Lage J. H.: Dietary and hormonal influences in experimental uraemia. J. Lab. & Clin. Med. 34 9... 1949.
14. Bluemle L. W., Jr., Potter H. P., and Elkinton J. R.: Changes in body composition in acute renal failure. J. Clin. Invest. 35 1094 1956.
15. Merrill J. P.: The treatment of renal failure. New York, 1955, Grune & Stratton, Inc.
16. Gjørup S., and Thaysen J. H.: The effect of anabolic steroid (Durabolin) in the conservative management of acute renal failure. Acta med. scandinav. 16... 1960.
17. Gjørup S.: Protein ... of glucose ... administered intracavally in patients with acute renal failure. Acta med. scandinav. 161 ... 1958.
18. ...ler R.: The danger of ... thy... ... Lancet 1 ... 1959.
19. Parsons F. M.: Haemodialysis ... indications ... Postgrad. M. J. 35 ... 1959.
20. W...tschinger ... and Watt... J.: Indication ... of kidney dialysis. Wien Ztschr. inn. Med. 41:61 1960.
21. Brown-Séquard C. E.: ... 1891. Cited by Kochakian C. D.: The sexual glands and metabolism. III. The influence of injection of testicular ... upon the nitrogenous metabolism of dogs ... Brit. J. Exper. Path. 6 ... 19...
22. Kochakian C. D., and Murlin J. R.: The effect of male hormone on the protein and energy metabolism of castrate dogs. J. Nutrition 10 437 1935.
23. Kochakian C. D., and Murlin J. R.: The relationship of the synthetic male hormone androstenedione to the protein and energy metabolism of castrate dogs and the protein metabolism of a normal dog. Am. J. Physiol. 117 642 1936.
24. Kochakian C. D.: Testosterone and testosterone acetate and the protein and energy metabolism of castrate dogs. Endocrinology 21 750 193...
25. Korenchevsky V., Dennison M., and Brovsin J.: The assay and the effect of testosterone on rats compared with those of other sexual hormones. Biochem. J. 30:558 1936.
26. Selye H.: The effect of testosterone on the kidney and on the general condition of uraemic animals. C. M. A. J. 42 189 1940.
27. Klotz H. P., and Debray J.: L'action de la testostérone sur le fonctionnement rénal. J. urol. 55 123 1949.
28. Dérot M., and Bernier J. J.: A propos du traitement des nephrites ... par la testostérone. Influence de la testostérone sur l'azotémie. Bull. Soc. méd. Hôp. Paris 66:205 1950.
29. Freedman P., and Spencer A. G.: Testosterone propionate in the treatment of renal failure. Clin. Sc. 16 11 1957.
30. Blagg C. R., and Parsons F. M.: The use of norethandrolone in acute renal failure from obstetric causes. Lancet 2:377 1960.
31. Brøchner-Mortensen K., Gjørup S., and Thaysen J. H.: The metabolic effect of new anabolic 19-nor-steroids. Acta med. scandinav. 165 197 1959.
32. Llaurado J. G., Trunnell J. B., and Clau... J. L.: Some effects of simultaneous administra

tion of norethandrolone and cortisone in the rat Acta endocrinol 32 536 1960

33 Landau R L Lugibihl K and Dimick D F Metabolic effects in man of steroids with progestational activity Ann New York Acad Sc 71 588 1958

34 Herrmann J B Kirsteim E and Krakewr J S Hypercalcaemic syndrome associated with androgenic and oestrogenic therapy J Clin Endocrinol 9 1 1949

35 Gjørup S and Thaysen J H Severe renal failure treated with anabolic 19 nor steroid Ugeskr Laeger 120 1499 1958

36 Sen D K Uraemia and its treatment by arginase inhibitor Nature 184 459 1959

Special report

Einthoven Symposium*

Opening remarks by Professor Dr H A Snellen

Ladies and Gentlemen it is a very great pleasure indeed to welcome you all at this symposium in honor of the centennial of Willem Einthoven on behalf of the organizing bodies the University of Leiden which can be proud to have had Einthoven among its professors for more than forty years the Boerhaave organization for postgraduate teaching the Dutch Physiological Society and the Dutch Cardiological Society I feel privileged to call on our Dean of the Medical Faculty Professor Gaillard to open this symposium by saying a few words to us

Opening words by Professor Dr P J Gaillard

Ladies and Gentlemen it is a great pleasure and honor to open the symposium As Dean of our faculty I welcome all participants and guests on behalf of the faculty of which Willem Einthoven was such an outstanding member

Those who remember Einthoven know that he thought as a sage and at the same time felt as a man As young students we often hesitated to approach him but once we did we always became impressed by his charm and by the fatherly way in which he formulated his advice

Therefore you will understand that we feel proud and happy that this symposium is going to be held in commemoration of him

I wish you a most successful and profitable day guided by the spirit of the man to whom we attribute our highest feelings of admiration

With these few words Ladies and Gentlemen I declare the session open

*Proceedings of the Symposium in commemoration of the birthday (May 21 1860) of Willem Einthoven, held Leiden, Netherlands, on Saturday June 25 1960 under the sponsorship of the University of Leiden and the Dutch *Physiological and Cardiological Societies.*

Developments in the physiology of color vision since Einthoven

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Soesterberg, Netherlands

In the nineteen twenties the necessity for a more rigid base for photometric brightness and color specifications and for the development of color reproduction greatly stimulated the development of more systematic research programs in color vision.

Since then there has been an increasing tendency to collect data about behavioral functions along a scheduled line by a group of investigators often from different specializations, rather than progress being made more exclusively and more incidentally by the ingenuity and manysidedness of individual persons. Einthoven stands as a representative and as a vivid example of the latter class of individuals just at the transition to this new look in scientific activity.

Since his death an enormous amount of accurate data on color vision functions has become available. Improvement in technical equipment has made a vast contribution to this progress. This is particularly evident in the case of the handling and measurement of spectral energy distribution and of electrical phenomena in neurophysiology, which nowadays can be done relatively easily and accurately with the aid of recently developed laboratory equipment.

However, with respect to what previous generations had already discovered or had already thought of, little progress has been made in so far as essentially new ideas are concerned.

The highlights in the historical development of the physiology of color vision since Einthoven can be discussed under three headings. In the first place there is the discovery of what I like to call two retinal directional effects.

In 1933 Stiles and Crawford from the Photometric Division of the National Physical Laboratories in London found that the color receptors in the retina—the cones—have a sensitivity that depends on the direction of the incident light. The same workers found in 1937 that this directional effect was also influenced by the wave length of the light. In 1937 Stiles also published extensive measurements he had made of another effect; it appeared to Stiles and Crawford that the apparent color also depends on the direction of the light incident upon the retina. Hansen from the Zeissworks mentioned that he had noticed this effect in 1929. Actually, it is very surprising that these effects remained hidden until the nineteen thirties.

Indeed, the influence that the eccentricity of the light falling on the pupil has on apparent brightness and on apparent color is far from small. On the average all through the spectrum for photopic vision in the fovea, sensitivity is about 4 times less for light coming 3.5 mm. ec-

From the Institute for Perception RVO-TNO, Soesterberg, Netherlands.
Received for publication [illegible]

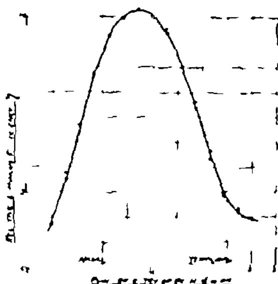


Fig. 1

centrically through the pupil than it is for light passing centrally (Fig. 1). This decrease in sensitivity goes with a change in apparent color that covers for the blue-green part of the spectrum as much as 10 mμ (100 Ångström) (Fig. 2). People with normal color vision can distinguish between wave lengths only 1 to 2 mμ apart in this region of the spectrum.

Einthoven and also Brücke came close to the discovery of both these effects when they studied the effect of chromatstereopsis as described by Donders. In this study Einthoven moved stenopaic diaphragms in front of the pupil. He demonstrated with this that for suitable positions of the stenopaic diaphragms the selfsame observer can see the red *in front of* blue as well as the reverse.

Recently Vos pointed out and reported at the September 1959 meeting of the Dutch Physiological Society that a reversed chromatstereoscopic effect can be obtained as well when the preferential direction of the cones is eccentric as compared with the axes of the eye. Probably eccentricity in pupil position and in directional preference of the cones contributes equally to the reversed chromatstereoscopic effect.

Anyhow, Einthoven's experiments with different locations of stenopaic diaphragms in front of the pupil when looking at objects of different colors represents the situation in which the Stiles-Crawford effects most easily reveal themselves.

Recently Campbell discovered a third retinal direction effect. *It refers to the* dependence of visual acuity on obliqueness of the light and can be left out of consideration here.

I now come to the second highlight in the development of the physiology of color vision in the last decades. It refers to the theory of color vision. A good many of the outstanding research workers share the opinion that almost all facts of color vision point to the necessity of accepting the existence of three fundamental response systems at the receptor level, of which the spectral sensitivity curves are very similar or equal to those proposed by Pitt. The bases of this view became even more firmly established when we recently succeeded in bringing both Stiles-Crawford effects under one explanation.

In this study, the results of which were also reported by Walraven at the September 1959 meeting of the Dutch Physiological Society, Pitt's set of curves was involved. I will not repeat fully the train of thought but considerable help came from Stiles' own speculation on the basis of his discoveries as well as from Brindley

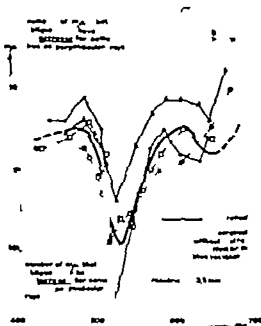


Fig. 2

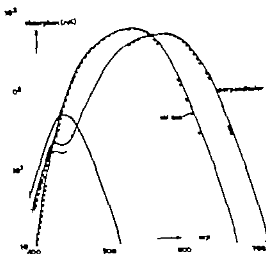


Fig 3

work on the change of color equations for different eccentricities in the pupil From this was developed the idea that in the outer segment of the cones with increasing obliqueness of the light an increasing fraction of the light leaks away to the surrounding tissue and does not further contribute to the perception Simplified it means a shorter effective pathway through the receptor for oblique light In the case of high concentration of the photo pigment shortening of the pathway narrows its spectral absorption curve (Fig 3)

For acceptable values of absorption power for perpendicular entrance of the light at the maximum of the spectral absorption curves both Stiles Crawford effects were quantitatively explained My belief is that this result is a very important one in favor of Young s idea of three types of color receptors in the fovea

Although most contemporary theorists now agree that the color vision system is based on a three variables mechanism dissident opinions frequently are expressed By and large these suggestions stem from the Hering opponent colors theory However this theory itself also contains a three variables mechanism the components being the antagonistic red green yellow blue and black white systems

An increasing amount of experimental data makes it probable that the Young Helmholtz and the Hering theory refer each to a single zone in the chain of events involved in color perception This idea of more than one zone of activity came from Donders

I shall mention briefly some of these experimental data First of all there is the work of Rushton He could prove the existence of photopigments by making measurements of the spectral reflectance of the retina under different conditions of adaptation obtained by strong illumination with light of different colors The changes he found in spectral reflectance are due to the bleaching of the visual pigments by the strong illumination The spectral sensitivities which he deduced for the pigments from these measurements are very much similar to Pitt s curves

Another important contribution came from Granit who with microelectrode techniques measured the electrical activity of retinal elements Elements of different spectral sensitivity curves were found pointing to the existence of different response systems in the retina This work is so generally known that there is no urgent need for extensive reporting of it here His modulators represent the Young Helmholtz type of receptors His dominator is an example of a mechanism that is more of the Hering type a brightness mechanism

Svaetichin recently found such a dominator also in the retinae of fishes The most remarkable point in his work however is that he also found nerve elements in these retinae with a spike activity exactly representing Hering s antagonistic color components He used microelectrode techniques Some nerve elements in his work demonstrated in some regions of the spectrum a positive electrical activity and in other regions a negative activity What type of nerve elements they were is not exactly known at least some disagreements of opinion are not yet solved Anyhow this type of elements is found and does exist in the retinae of fishes It might be that this phenomenon is strictly related to the existence of twin cones in these retinae

It is encouraging that some of the most outstanding theorists—such as Judd for instance—are convinced now of the possibility of integrating Hering s and Young Helmholtz s hypotheses on the basis three variables mechanisms in some

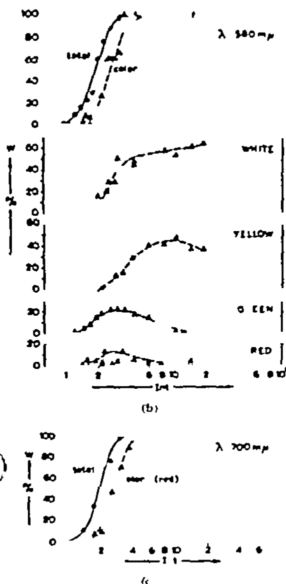


Fig 4

of zone theory For instance it has been shown by Judd that Müller s zone theory is quite consistent and can be used to explain a good many of the facts in color vision

The third main point to which I would like to draw your attention is also theoretical in nature Around 1900 Planck made the final discovery of the corpuscular nature of light It was not until 1915 that it was asked whether and how in the physiology of the visual system this quantum nature is revealed Mutual discussion between Lorentz and Zwaardemaker resulted in Zwaardemaker s speculative suggestions that the active energy needed in order to reach the threshold is fulfilled for the nervous system when two quanta are absorbed In 1944 this hypothesis was given a more substantial foundation by van der Velden with the aid of ingenious theoretical statistical considerations and with related experiments to back them up The basic idea of this quantum theory in vision is that statistical fluctuations in the flux of quanta are apparent in perception and are reflected in the threshold mechanism

As a result of the work of van der Velden and others it became a generally accepted fact that a rod is activated by the absorption of one quantum The same can be concluded for the cones Two such absorptions sufficiently close together in time and space result in a perception Although these more precise threshold conditions are considered by some authors to be rather speculative and not very well established others have proceeded along the lines suggested by quantum theory for further development of these ideas Recently it was proved that an analysis of the instability in color identification near the threshold of vision is possible in terms of the quantum theory (Fig 4) Walraven reported work on this subject in the June 1958 meeting of the Dutch Physiological Society It was found that a twofold coincidence of quanta in the cones does not always result in a color perception It frequently produces only an achromatic sensation In the red the mechanism responsible for a red appearance starts to work in a twofold coincidence basis (Fig 5)

Some more considerations of this type were abstracted from the experiments. Quantum theory has already been applied for the description of various visual functions like threshold dependence on size and exposure time and on velocity in the case of a moving target It also described the dependence of visual acuity on brightness and furthermore it has been extended by de Vries and Rose to explain the dependence of contrast threshold on brightness It is worth while to consider this point a little further It was suggested by de Vries and Rose—and this was confirmed by earlier experiments—that differences in apparent brightness occur when physically

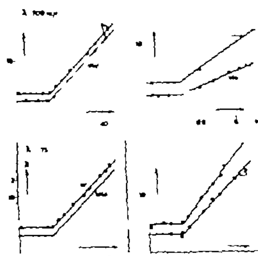


Fig 5

the difference between the intensities is significant It means that the intensity difference between the stimuli must exceed the statistical differences in the quanta numbers between both

Very recently we tried to describe also just noticeable differences in color on similar assumptions It proved that color vision functions in such a simple case as tritanopia can easily be explained in this way The base for this argument is that two stimuli can be distinguished when the collections of statistically possible combinations of quantum numbers absorbed in the three color receptor systems n n n_3 do not overlap Again P tt s fundamental response curves were taken as a basis for the three receptor systems

At least quantum theory might prove to have the same merits as the photochemical theory proposed and developed by Hecht (1937) This theory kept researchers working on systematic projects for some time However it is not hoped that the criticism that can be leveled at Hecht s photochemical theory never can be applied to quantum theory I point here to the very fact that before Hecht expressed his theory the basis of it could already be considered as being disproved Indeed Zwaardemaker and Lorentz found before 1919 that very few quanta are involved in the visual process and that these few moreover are distributed over several receptors In that case application of the mass action law for chemical reactions to the photochemistry in the receptors is of little value Hecht himself (1942) became also the first pioneer for the quantum type of approach in visual theory in 1940

REFERENCES

1 Bouman M A J Optic Soc Am 4 36 195
2 Brindley G S J Ph siol 122 332 1953
3 Brucke E Sitz Ber Kaiserl Akad v Wiss Wien M th Natw Klasse II 58 321 1868
4 Campbell F W J Physiol 143 25 1958
5 Donders F C Abstract Arch Ophthalmol 27 155 1881
6 Einthoven W Graefes Arch Ophthal 31 10 1885
7 Granit R Sensory mechanisms of the retina London 1947 Oxford University Press
8 Hecht S Physiol Rev 1 239 1937
9 Hecht S J Optic Soc Am 32 42 1942
10 Judd D B J Res Nat Bur Standard 42 1 1949
11 Rose A J Optic Soc Am 38 196 1948
12 Rushton W H Visual problems in color Proc N P L Symposium 1957
13 Stiles W S and Crawford B H Proc Roy Soc Ser B 122 418 1933
14 Stiles W S Proc Roy Soc Ser B 123 90 1937
1 Stiles W S and Crawford B H Nature (London) 139 246 1937
16 Stiles W S Proc Roy Soc Ser B 127 64 1939
17 Svaetichin G Ann New York Acad Sc 74 385 1958
18 Van der Velden H A Ophthalmologica 111 321 1946
19 Van der Velden H A Physica 11 179 1944
20 Vos J J J Optic Soc Am August 1960
21 de Vries Hl Physica 10 553 1943
22 Walra en P L and Bouman M A J Optic Soc Am July 1960
23 Z aardemaker H Leerboek der Physiologie Haarlem 1920 Bohn

Ion movements underlying the cardiac action potential

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The years of 1902-1903 are marked by Einthoven's publication[1] of the first surface electrocardiograms which for all practical considerations may be called undistorted (Fig. 1). Before and after this date it has been recognized that the electrical variations recorded from the surface of a body are composite in nature. Consequently much effort has been made to obtain the potential time course from the site of its origin, the surface membrane of cardiac fibers. In 1883 Burdon-Sanderson and Page[2] were leading off between an injured and a noninjured spot of the frog or tortoise heart and obtained the first monophasic records by means of a fast moving capillary electrometer. Such tracings are currently interpreted to reflect the variations taking place in the intact part of the heart; it is assumed that the damaged region makes no contribution. Schutz in 1929 found the means to keep one spot injured permanently by the combined effect of a ligature and suction. This technique made it possible to obtain reproducible records over longer periods of time and gave rise to systematic investigation of the monophasic action potential under a variety of conditions.[3]

The recording of membrane potentials

It was in 1949 when the problem of the recording of potentials was brought one step further. Ling and Gerard described their microelectrodes which could be inserted into the inside of a single muscle fiber, thus making possible the recording of a potential difference across the surface membrane, *the transmembrane potential*. The lower half of Fig. 1 illustrates the procedure and results. With the tips of two microelectrodes on the heart surface a reference potential is first recorded. One of the two electrode tips (diameter about 0.2 μ) is then pushed into a single fiber (diameter about 16 μ in mammalian heart). The potential jumps to a new steady value. This indicates that during diastole the inside of every fiber is negative by about 90 mV with respect to the fiber surface, *resting potential*. When the heart is stimulated a monophasic *action potential* results. To illustrate the temporal relationship with the surface electrocardiogram, the upstroke of the monophasic curve has been made to coincide with the beginning and the downstroke with the end of the ventricular complex (Q and T respectively). The changes in potential that can be obtained at the level of a single fiber are about 100 times larger than those present in a surface ECG. It is noteworthy that during the first phase of activity the monophasic curve "overshoots" the reference line. This means that the inside of single fibers becomes positive with respect to the outside. It should be added—even in a talk given at Leiden—that this phenomenon was first

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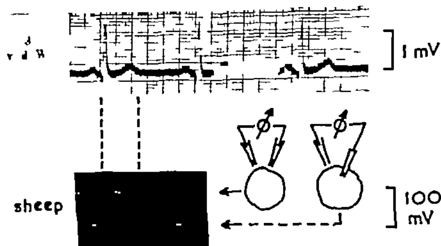


Fig 1 *Upper record* Electrocardiogram of subject d W taken with Einthoven string galvanometer published in 1903 Time marks are 40 msec apart *Lower record* Transmembrane action potential of sheep myocardial fiber The two records have been arranged so as to make the upstroke of the transmembrane action potential coincide with the Q wave and the down troke with the T wave of the lectrocardiogram

described by Engelmann Nuel and Pekelharing working at Utrecht They were leading off between a noninjured and an injured spot and making contact with a slowly moving galvanometer for short periods at different phases of activity With a resting heart the galvanometer moved in one direction in the beginning of cardiac activity the galvanometer moved appreciably in the other direction

At this point it seems appropriate to show a record correlating the electrical and the mechanical activity In Fig 2 the electrical record was obtained with a Ling Gerard electrode the mechanical record (from a whole turtle ventricle) by making use of a mechano-electrical transducer (RCA 5734) In cooled turtle hearts the action potential resembles a square pulse Mechanical shortening starts shortly after depolarization relaxation starts with a sharp kink when the membrane repolarizes

The distribution of ions

Ionic order (Fig 3) represents stored energy Ion gradients make it possible for strong membrane currents to flow during certain phases of activity whereas metabolic energy will be required during other phases of the cardiac cycle to re establish the ion gradients

According to analytical data potassium ions are accumulated in the cardiac myoplasm by a factor of about 30 whereas sodium ions are present at a concentration 10 times lower than in the interspace (see Reference 7)

Little quantitative information is available on the rate of exchange of ions between the inside of cardiac fibers and their environment The half time for potassium exchange as measured by the aid of tracer K is of the order of 1 hour As to sodium there is evidence to suggest that

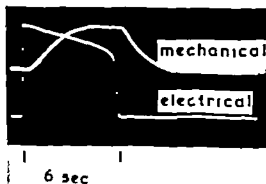


Fig 2 Temporal relationship between monophasic action potential and contraction Turtle heart t 8 C The upstroke and the downstroke of the action potential are retouched From Weidmann

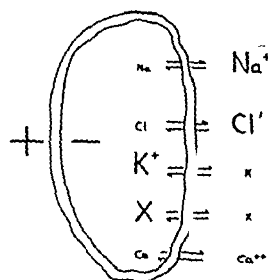


Fig. 3. Distribution of ions between the intracellular and extracellular spaces. The intracellular anions are not fully identified and are therefore denoted by X. Concentration ratio and half time for tracer exchange (minutes) respectively: Na 1:10 ... 1:0; Cl 1:30 ... 1:(?); K 30:1 and 60; Ca ... and ( ).

the permeability of the surface membrane at rest is lower than that to potassium ions, both from electrical data[7] and from tracer measurement.[8] Electrical data also suggest that the chloride permeability of the resting membrane is low as compared to the potassium permeability.[9]

Sodium ions have to be extruded from the fibers against both a concentration gradient and an electrical gradient. For thermodynamic reasons this must depend on metabolic energy. Accumulation of potassium may for theoretical reasons be a passive process depending on the voltage gradient established by sodium extrusion, but it is questionable whether or not a large proportion of potassium inflow depends, as shown for nerve fibers,[3] on the availability of metabolic energy.

Ion movements during activity

Nerve physiologists have since the end of the second World War made an important contribution to physiology as a whole by identifying the ionic species that are shifted between the intracellular and extracellular spaces in different phases of the action potential.[3] The results may be summarized by saying that an influx of Na^+ ions is responsible for the upstroke of the action potential (depolarization and overshoot), whereas a net outflux of K ions brings about repolarization. Cardiac electrophysiologists have been busy testing how far the results obtained on peripheral nerve fibers are applicable to the heart.

It was noticed already by Overton[1] in 1902 that the frog heart becomes unexcitable when the extracellular concentration of sodium drops below 10 per cent of its normal value (substitution of NaCl by saccharose). More recent experiments have confirmed this finding for sheep and calf myocardium.[1] Furthermore, the electrical changes observed (Fig. 4) are in agreement with the hypothesis that the membrane at rest is sparingly permeable to sodium ions but undergoes an important increase in permeability when activated. If part of the NaCl is replaced by choline chloride (choline being a nonpenetrating ion), there is (a) no change of the resting potential, (b) a decrease of the overshoot, (c) a decrease in duration of the action potential, and (d) a decrease in the upstroke velocity of the action potential (not seen in Fig. 4).

The view that repolarization in cardiac muscle is due to an increased outward movement of potassium ions is supported by tracer data. Fig. 5 shows the ^{42}K outflux from the coronary system of a turtle heart which had previously been loaded with ^{42}K. The curve has been corrected for the travel time in the vascular system



Fig. 4. Effect of substituting choline chloride for 80 per cent of the NaCl. Successive action potentials of the same ventricular fiber of a sheep heart. The camera was opened during the first 30 sec. of perfusion with the sodium poor solution, then again between 60 and 90 sec. Upstrokes of the superimposed action potentials have been retouched. From Délèze.[11] (By permission of American Heart Assn., Inc.)

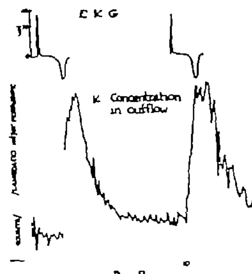


Fig 5 Rate of outflow of ^{42}K from turtle ventricle in the course of two heartbeats From Wilde[16]

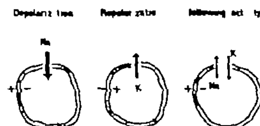


Fig 6 Movement of ions in different phases of the action potential

as well as for changes in rate of flow during contraction It shows (a) that there is ^{42}K outflux even from the resting heart and (b) that there is a large increase of K outflow synchronous with the T wave of the electrocardiogram i e synchronous with the phase of repolarization of the monophasic action potential

The ionic movements are summarized in Fig 6 Inward current of positive charge (sodium ions) causes depolarization and outward movement of positive charge (potassium ions) causes repolarization These currents result in a slight increase in the intracellular concentration of sodium and a corresponding decrease in intracellular potassium In the turtle heart the loss of potassium ions associated with a single beat is estimated at 1/400 of the total intracellular content[1] To keep the system in equilibrium the ions exchanged during the action potential have to be pumped back and it seems reasonable to assume that this happens mostly during diastole

The experiments presented so far indicate that qualitatively the cardiac action potential can be explained on the same basis as the nervous action potential Nevertheless there is an important difference of a quantitative nature activity in nerve lasts for less than 1 millisecond whereas the action potential of a mammalian ventricle has a duration of 200 to 300 milliseconds The simplest way to account for the difference is to assume that the permeability to potassium of the surface membrane rises rapidly when nerve fibers are depolarized but rises with a considerable delay when myocardial fibers are depolarized Measurements of the electrical resistance of the surface membrane would agree with this hypothesis for it can be shown that throughout the myocardial action potential the resistance is high indicating a low permeability to ions[17]

Concluding remarks

Looking at the results obtained during the past decade we may say (1) The absolute values of the cardiac resting and action potentials have been determined with a fair amount of accuracy thanks to the microelectrode technique (2) Reasonable interpretations have been made to correlate the measured membrane potentials and the data on the distribution of ions (3) In a qualitative way electrical activity in heart tissue seems to occur on the same basis as that in nerve tissue (4) The data on the movements of ions in the heart are scarce so far and much remains to be done until the cardiac action potential can be accounted for in a quantitative way in terms of ionic currents

REFERENCES

1 Einthoven W Die gal anometrische Registrierung des menschlichen Elektrokardiogramms zugleich eine Beurtheilung der Anwendung des Capillar Elektrometers in der Physiologie Pflüger Arch 99 472 1903
2 Burdon Sanderson J and Page F J M On electrical phenomena of excitatory process in heart of frog and of tortoise investigated photographically J Physiol 4 327 1883

3 Sch t E Elektroph iologie des Herzen bei einph scher Ableitu Ergeb Phys iol 38:193 1936
4 Ling C nd Gerard R W The norm l mem br ne potential f frog sartorius fibers J Cell & Comp Ph ol 34:383 1949
5 E gelm nn T W N et nd Tekell tm Over de lectromot rische erschijnsele het h rt Proc erlu l Kon Akd Wetensch t Am terd m 29 3 J ne 5 18 3
6 W idm S Electrical event derl ng the card c cont act m In C cul t Proceeding f the H rvey T rcentenary C ngres Oxf rd 1955 Blackw ll pp 100 109
7 Weidma S Elektroph l gie der Herz m k H ser Berne nd Stutt rt 1956 Huber
8 Carmeliet E E nfluence d l concentrat n extracellul re d K r l perm' l lté de l meml rane des fil res de Purki je de mouton pour l s ons K H l et physi l & ph rmacol cta 18 C15 C16 1960
9 Schreib r S S Pot ium and sod um ex h ng tl work ng frog heart Effects of overwork external concentration of pot ium l l um Am J Physiol 184 337 1956
10 H tter O F nd Noble D The influence of anions on impulse generation and membrane conduct nce in Purk je l myocardial fibres J Phy l 14 161 171 1959
11 Carmeliet E Effet de la ubst tution des io chlorure sur le potentiel de membrane des fi res de P k je Helv et physi l pharma col act 1 C18 1959
12 H l km A L nd Keynes R D Acti tra port of cat ons in gia t ns from Sepia H l J Ph l 128 8 1955
13 H l k A L Ionic movement nd electrical act ty gia t nerv fibres Proc Roy Soc Ser B 148 1957
14 Overton E Beiträ zur al emeinen M k l Nervenphysiol ie l ff er Arch 92:346 190
15 D l re J Terf m of trip f mammalian entricl Effect f K rich l N -deficient sol t on on t n membrane potential C cu l t on R 101 1959
16 W l le W S Th p ibat k nature f the rele se f pota sium from h rt muscle d ring the t le New Y rk A ad Sc 6 Art le 6 p 693 Au 9 195
1 Cor boeuf E Zacout F C rgouil Y M l Lapland J Mesure de la ré tance membra ire du my rde entriculaire de m mmif res au ours de l act té C mptes ren lus Acad Sc Par 246:2231 1958

The electrocardiogram in normal and some abnormal conditions

In revived human fetal heart and in acute and chronic coronary occlusion

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Nearly 55 years ago a telephone wire connecting Einthoven's laboratory with the internal clinic made it possible to register electrocardiograms from patients. After some time this connection was severed by the clinician. It must have been a strange idea indeed that a machine could give information about the patient not detectable from direct contact with the patient. In many respects this interruption may be considered a symbolic action. Electrocardiography as a part of physiology and electrocardiography as a part of clinical medicine had to go a separate way for a long time before reunion took place.

The group I represent here is nearly completely composed of persons interested in clinical medicine. Our work started in 1947 with the study of the transmural and intramural potentials in the dog and the goat. But our main target, the human heart, was not accessible. Only in the last year did we find a method suitable to investigate the exposed heart of the human being in a satisfactory way.

Experimental approach

A. Heart. The explorer of the electrical aspects of the heart is faced with many difficulties. How can he accomplish his main purpose, the unraveling of cardiac excitation, in such a way that his approach does not change the phenomena he wants to investigate? Two lines of approach are possible. One means is exposition of the heart by thoracotomy. Probably the complexes registered from the exposed heart are not identical with the complexes from the heart in the intact thorax. The second approach is the Langendorff perfusion of the isolated heart, a method which for the human heart was used for the first time by Zbyszewski and perfected by Boden and Neukirch.

B. Electrodes. Three kinds of electrodes were used: (1) Differential electrodes to record local phenomena. This type of

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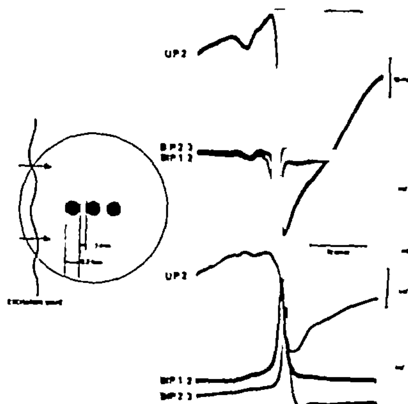


Fig 1 Three terminals 1 3 a distance of 0 1 mm apart were placed on the epicardial surface of the heart in region in which the excitation wave progresses from terminal 1 to 3 A point on the fast portion of the intrinsic deflection in unipolar complex from the middle terminal coincides with the point of intersection of the bipolar complexes

electrode consists of two electrodes lying very close together for example 0 1 millimeter apart (2) Small tipped unipolar electrodes for extensive exploration of the epicardial and endocardial surfaces of the heart (3) Intramural needle electrodes

Apparatus A four channel high fidelity oscillograph with separate recording and viewing tubes was used

Intrinsic deflection and local excitation Our previous investigations[3,4] have shown that the electrical effects of local excitation can be best studied by means of differential electrodes It can be demonstrated how ever that the electrical effects of local excitation can frequently be discovered in the unipolar records A differential electrode with three terminals at a distance of 0 1 millimeter was placed on the epicardial surface on an area where the excitation process spreads from 1 to 3 (Fig 1) The complexes between 1 2 and 2 3 are very similar The intersection of bipolar complex 1 2 with complex 2 3 signals the arrival of the excitatory wave at terminal 2 coinciding in the unipolar record with a point on the rapid part of the intrinsic deflection For the measurement of time relations only the rapid portions in the complexes are used

Contrary to the opinion of some investigators we found that the location in the QRS complex of the electrical effects caused by local excitation is not constant It may differ in complexes from different areas of the heart (Fig 2) The effects of local excitation are represented by a fast deflection which may occur near the middle of the downstroke of the R near the top of the S On the ascending limb of the S it may appear as a negative going potential In some areas mainly on the posterior wall we even found the effects of local excitation on the ascending limb of the Q

Total excitation of dog heart

Total excitation of the heart of the dog, the experimental animal commonly used, is now rather well known.[4-7] I will comment on only a few points. During the study of the sinus node and A-V node we were impressed by the sensitivity of these structures to pressure of the exploring electrode. Even slight pressure on the sinus node caused disappearance of the multiphasic electrical activity specific for these structures. The introduction into the sinus node of a needle electrode of the type we used caused a complete disappearance of multiphasic activity.

Specific tissues of heart. The electrical activity of the main branches of the bundle of His can be seen as multiphasic deflections preceding the cavity potential.

The pattern recorded in the subendocardial branches of the Purkinje system is somewhat different: mostly only one or two spikes are found. We could find no appreciable delay between the spikes caused by activity of the Purkinje fiber and the beginning of the myocardial depolarization complex after the Purkinje depolarization.

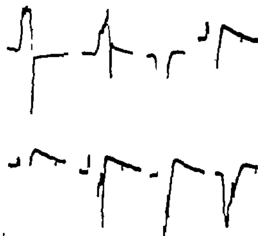
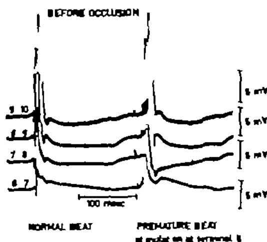


Fig. 2. Different locations of intrinsic deflection in QRS complexes. Unipolar complexes from different regions of the removed heart of a 7 month-old human fetus. The effect of local excitation can occur in the downstroke connecting top R with nadir S, near the top of the S, on the ascending limb of the S and ascending limb of QS complex registered from the posterior side.



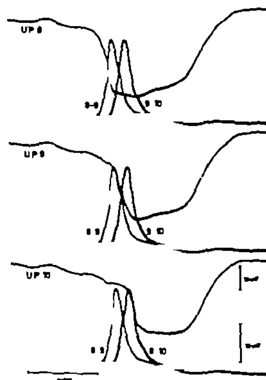


Fig. 3. *Top.* Bipolar complexes during normal beat followed by premature beat caused by stimulation of terminal 5 situated in the subendocardial layer. *Bottom.* Bipolar complexes in outer layers of ventricular wall with unipolar complexes from the terminals between which the bipolar complexes are recorded. The intrinsic deflection in unipolar complex 8 is synchronous with the fast portion in upstroke of bipolar complex 8-9. In unipolar complex 9 the intrinsic deflection is synchronous with the intersection of the downstroke in 8-9 and the upstroke in 9-10. In unipolar complex 10 the intrinsic deflection is synchronous with the downstroke in 9-10. The duration of the bipolar complexes is approximately 5 milliseconds.

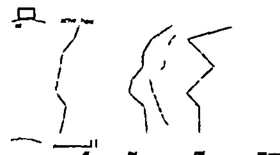


Fig. 4. The time of activation in the intramural layers was measured by the time of occurrence of the intrinsic deflection in unipolar and bipolar records. A.R.P., the absolute refractory period; T.R.P., the total refractory period, the duration until cardiac excitability has regained the diastolic level; F.R.P. is the functional refractory period, the period after which the myocardium is capable of conducting a propagated excitation wave. The time course of F.R.P. rather closely follows activation time.

The Purkinje system distributes the excitatory wave in 5 to 10 milliseconds to all subendocardial parts of the ventricles.

The question of the presence of intramural extension and the degree of intramural extension of the Purkinje network is not solved. In previous experiments we gave only indirect evidence for the existence of an intramural network of the inner layers of the ventricular wall in the dog. For many years we looked for evidence of electrical activity of the Purkinje system in the left ventricular wall, but never found it. We did find it, however, in the goat. Here we could record Purkinje activity preceding the muscular depolarization complex in bipolar intramural records at different intramural layers, even in the subepicardial layers. The intramural extension of the Purkinje network is proved conclusively by Meyling and Ter Borg.[8]

Intramural excitation. In the outer layers of the ventricular wall the excitatory process progresses with nearly constant velocity, approximately 50 cm. per second, toward the epicardial surface. The region in which depolarization takes place appears to be very sharply defined. The electrical effects caused by this wave can be represented by a polarized surface. The distance between sources and sinks is 1 mm. maximum. The drop in potential across this wave is at least 15 mV (Fig. 3).

Ventricular septum. The ventricular septum is activated from both sides.[1, 12] No functional boundary between the portion supplied by the right and left bundles can be demonstrated.[1] The basal regions of the septum are activated latest in the cardiac cycle; therefore, the excitation wave in the ventricular septum progresses in an apico-basal direction.

The excitatory process in both ventricles progresses toward the posterobasal region, which is activated latest in the cardiac cycle.

Repolarization. The pathways of the repolarization process cannot be investigated with the methods so successfully applied in the analysis of the depolarization process. Opening of the thorax changes the T waves. Because of the gradual character of the repolarization process, the arrival of this process at the exploring terminals cannot be identified. We have tried to follow the pathways of the repolarization process, using the duration of the functional refractory period (F.R.P.) as a measure of the time necessary to restore cardiac excitability. At the end of the F.R.P. the myocardium resumes its ability to propagate an excitatory process. Since we could prove that at this particular moment the stimulating requirements are one and one-half times the diastolic level, the duration of the F.R.P. can be measured readily from strength-interval curves.[13] The duration of the total refractory period, however, cannot be determined accurately. The duration of the F.R.P. shows slight differences in the successive layers of the ventricular wall, up to ±15 milliseconds. It can be seen (Fig. 4) that the end of the F.R.P. follows more or less closely the pathways of depolarization.

Intact human heart

The clinical cardiologist is mainly interested in the excitatory process of the normal and pathologic human heart. Even in this era of cardiac surgery, adequate analysis of the human heart is difficult and mostly impossible. An extensive analysis of the human heart during operation takes such a long time that the safety of the patient may be jeopardized. Therefore, we used the Langendorff perfusion of the revived human heart.[14]

Reviving. We immersed 3 fetal hearts, each 7 months old, in a large container and

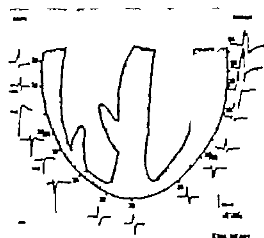


Fig 5A Sagittal section of the ventricles just to the left of the ventricular septum The numbers indicate the time of arrival in msec. of the excitatory wave at the epicardial surface Reference beginning of ventricular depolarization.

used as reference electrode a large one situated at least 8 cm from the heart Therefore the potential fluctuations of the reference electrode are very small in comparison with those of the exploring electrode and the records may be called unipolar The perfusion fluid had no oncotic pressure so that slight swelling of the heart caused by interstitial edema occurred Boden's and our own experiments support the conclusion that the excitatory process of the heart in situ and that of the isolated heart are very similar Records were made from 100 or more points in all hearts and after the experiment these points could be identified on the epicardial surface of the heart

Form of epicardial complexes There are no typical patterns for the left or right ventricle Complexes of the rS type are found near the attachment of the anterior papillary muscle of the right ventricle but also at the anterior surface of the left ventricle (Fig 5)

Complexes of the qR type are present on the left ventricle on two areas e g the anterolateral portion of the left ventricle and the high posterobasal area near the left atrium But qR complexes are also found on the right ventricle on the left lateral and high anterolateral area and the posterobasal area These complexes show initial negativity We may conclude that the patterns which up to now have been considered typical for the right ventricle and left ventricle are also found on some portions of the heterolateral ventricle

The form of the epicardial complexes at corresponding anatomic areas shows a striking correspondence I may mention the opinion of Boden and Neukirch after their experiments on the isolated human heart that the differences in the electrocardiograms of normal persons are probably caused mainly by extracardiac factors

The posterior and lateral surfaces of the left ventricle show Q waves as could be expected But also the posterior surface of the right ventricle shows initial negativity The area showing Q waves is located therefore at the posterior and lateral parts of both ventricles

These Q waves all begin at the same time in the cardiac cycle and probably at the beginning of the left ventricular cavity potential Their depth varies The Q is deepest about one third of the way from apex to base The deepest Q waves all are present on the posterior attachment of the ventricular septum and near the attachment of the posterior papillary muscles of the right and left ventricles (Fig 6)

To demonstrate this relation in still another way a section was made in the left ventricle parallel with the ventricular septum and just to the left of it (Fig 5B)

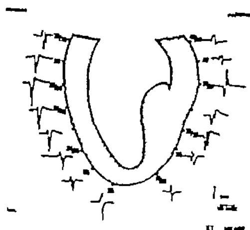


Fig 5B Frontal section of the ventricles just to the left of the ventricular septum The numbers indicate the time of arrival in msec. of the excitatory wave at the epicardial surface Reference beginning of ventricular depolarization

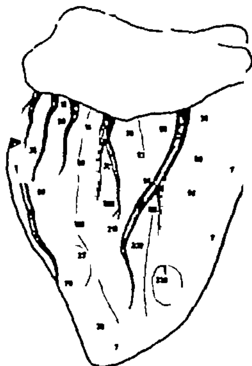


Fig 6 Posterior view of the fetal heart The numbers indicate the depth of the Q wave (in microvolts) in unipolar complexes from these places Deepest Q waves are present one half of the way from apex to base in the area overlying the posterior attachment of the ventricular septum The attachment of posterior papillary muscles is indicated too.

The relation of the Q and the papillary muscle is evident It is probable therefore that two factors at least contribute to the genesis of the Q wave (1) excitatory wave in the ventricular septum progressing in an apico-basal direction and (2) activation of the papillary muscles from their bases to apex

Epicardial excitation pattern The time of occurrence of the intrinsic deflection if well developed was measured in all records All measurements were corrected to the beginning of the Q at the posterior surface The times of arrival were grouped in 5 millisecond intervals The first epicardial break through occurs at the area trabecularis At each 5 millisecond interval an enlargement of the epicardial area activated is seen The anterior and posterior attachments of the ventricular septum appear to form no boundary for the epicardial excitation wave Epicardial excitation occurs latest in the posterobasal region of both ventricles

Elsewhere we described epicardial excitation as a double envelopment of the surfaces of both ventricles [14]

Many years ago Lewis[15] published a figure representing his considered view on excitation of the human heart It is evident from Fig 5A that there is a remarkable similarity between Lewis considered view and our findings

These conclusions are valid only for the 7 month-old fetal heart We hope to repeat these experiments in the adult heart in the near future

Let us now turn to abnormal excitation Because of our clinical interest we studied the changes occurring during acute coronary occlusion and in myocardial infarctions 4 to 14 weeks old

Acute coronary occlusion

Epicardial excitation pattern In the ischemic area all epicardial complexes show S-T elevations and abnormal Q waves In contrast epicardial excitation of the normal tissue surrounding the ischemic area remained constant up to 12 hours after the beginning of occlusion i e up to the end of the experiment

The epicardial surface of the ischemic area is activated late up to 50 milliseconds in the cardiac cycle This delay is caused

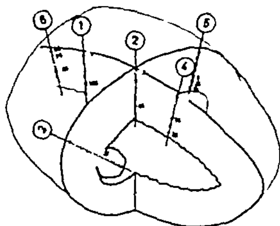


Fig 7 Coronary occlusion during 2 3 hours Spatial view of two cross sections of the left ventricle The numbers at the epicardial surface indicate the needle electrodes The smaller numbers at the intramural terminals indicate the degree of S-T shift measured (in mV) immediately after ventricular depolarization Needle electrodes 2 3 4 and 5 have the highest degree of S-T shift in the subepicardial layer

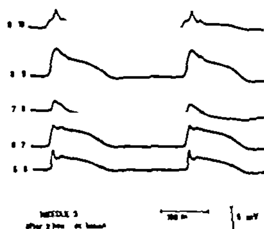


Fig. 8. Intramural bipolar complexes 2 hours after beginning of coronary occlusion. The complexes show large reduction in voltage and are notched. The S-T shift present points to the presence of gradient of injury making the outer layer positive in respect to the inner one.

by the decrease in conduction velocity of the excitatory process in the ischemic area.

The occurrence of premature beats during coronary occlusion is well known. In one case in which we followed the changes in electrical activity during coronary occlusion for 12 hours premature beats occurred which showed a constant form of the epicardial and intramural complexes. They were presumably caused by activity of a constant focus. Because these premature beats remained present for a few hours a complete epicardial excitation pattern could be recorded. The excitatory wave from this focus had the earliest epicardial break through at a region which appeared to be on the boundary of the infarcted area. Therefore the focus was situated in the area of transition between the ischemic and normal myocardial tissue.

Intramural excitation pattern. In all instances S-T segment elevation was present in all unipolar leads from intramural terminals situated in the ischemic area but the degree of S-T shift varied (Fig. 7). The S-T shift was measured at the end of ventricular depolarization in the ischemic area. At many places maximal S-T shift was present in the subepicardial layers (needle electrodes 2, 3, 4, 5) and at other places in the mid mural layers (needle electrode 6). A few hours later S-T shift at needle electrode 2 was maximal in the subendocardial layers.

In the intramural layers of the ventricular wall surrounding the ischemic area we could never reach a negative side of the boundary responsible for the S-T shift. S-T depression however was always found in the left ventricular cavity at the opposite side of the heart. We think that a sharply defined boundary is not present but that there is a very gradual transition between injured and noninjured fibers.

Bipolar intramural complexes. During occlusion the bipolar complexes registered between successive intramural terminals changed profoundly but the observed changes did not follow a constant pattern.

The diameter of the coronary vessel occluded varied in different dogs and the role of the collateral circulation responsible for the maintenance of a reduced blood supply could not be ascertained. It is not possible therefore to give an adequate description of the changes of the excitatory process as a function of the changes in blood supply.

The bipolar complexes may change in different ways. In some cases only broadening of the bipolar complex was found. In

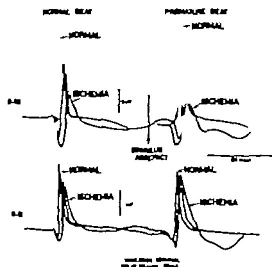


Fig. 9. Bipolar complexes 8-9 and 9-10. The complexes labeled *ischemia* were recorded 5 minutes after beginning of coronary occlusion. A negative deflection precedes small and broad positive deflection falling late in the cardiac cycle. They retain their form during endocardial stimulation. The complexes labeled *normal* were recorded 22 seconds after release of coronary occlusion. The transition of the abnormal complexes to normal intramural complexes can be clearly seen.

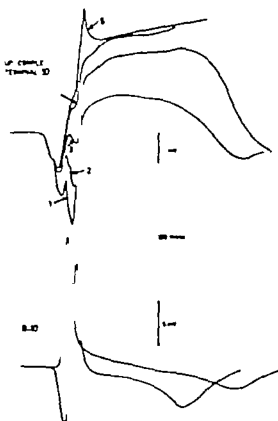


Fig. 10. Changes in complexes during progressive coronary ischemia. Complex 1 was recorded 15 seconds after beginning of coronary occlusion; complex 2, 60 seconds; complex 3, 100 seconds; complex 4, 120 seconds; complex 5, 135 seconds after beginning of coronary occlusion. The arrows indicate the location of the intrinsic deflection. Bipolar complex 1 was registered synchronously with unipolar complex 1, complex 2 synchronously with unipolar complex 5. The downstroke of the R in unipolar complex 5 occurs synchronously with the downstroke in 9-10 and is caused by excitation of muscle layers in contact with terminal 10.

other cases there was a loss of voltage in the bipolar complexes, but this change was always associated with broadening of the bipolar complexes. Fig. 8 is a typical illustration. The complexes are broad and show loss of voltage, notching, and S-T shift. The broadening of these complexes is caused by a diminished conduction velocity of the excitatory process in the ischemic area—sometimes 10 cm. per second or less. The loss of voltage can possibly be related to a reduction of the membrane action potential. The notching may be caused by the fact that the muscle fibers in the ischemic area are not changed to a similar degree by anoxia and do not conduct the excitatory process at the same rate.

Sometimes, and most frequently after the occlusion of a major branch or after prolonged occlusion of the coronary vessel, complexes of a perplexing form are found (Fig. 9, complex labeled *ischemia*). These bipolar complexes show a large reduction in voltage of the R, and a large negative wave precedes the R. Sometimes this R wave may disappear and the complex is completely negative.

Bipolar complexes of this type may even be present in successive layers of the ventricular wall. The changes which occur after restoration of blood supply may shed some light on the genesis of these complexes (Fig. 9). It can be seen that the depth and duration of the negative wave diminish. Simultaneously, the positive deflection increases in voltage and also falls progressively earlier in the cardiac cycle. After 20 to 30 seconds it is very high again and only a small negative wave precedes the positive deflection; the complex has regained its preocclusion form. It is an astonishing fact that the disappearance of the ischemic complexes occurs very rapidly, mostly within one half to one minute after the coronary circulation has been re-established. During that period multiple ventricular premature beats frequently occur. Many experiments terminated in ventricular fibrillation during that period.

It is possible that these bipolar complexes are caused by an increase in distance between sources and sinks of the polarized surface which represents the electrical effect of excitation.

Changes in unipolar epicardial and intramural complexes. During acute occlusion the form of the QRS complex of the unipolar epicardial complexes[4,14] and, as we could prove, also of the intramural complexes changes in the following manner: (1) decrease in voltage of S, sometimes even disappearance of the S; (2) a gradual delay in the onset of the intrinsic deflection; (3) decrease of the voltage and duration of the intrinsic deflection; and (4) perhaps complete disappearance of the intrinsic deflection.

Fig. 10 depicts the changes in the form of the unipolar intramural complex during coronary occlusion. The intrinsic deflection demonstrates the changes just described.

In the complex 4 the intrinsic deflection has disappeared only a small notch is present on the ascending limb of the monophasically deformed complex. One might be led to conclude that the excitation wave does not reach this terminal anymore.

However because the bipolar complex 9 10 shows a downstroke caused by excitation of 10 this conclusion is wrong. Therefore the disappearance of the intrinsic deflection does not necessarily mean that no excitation of the ventricular muscle in contact with the exploring terminal occurs. With prolonged ischemia the upstroke increases and upright deflection of short duration appears (complex 5 Fig 10) followed by a slow downstroke coinciding with the last portion of the descending limb of the bipolar complex 9 10. This deflection in the unipolar complex therefore is caused by local excitation at terminal 10.

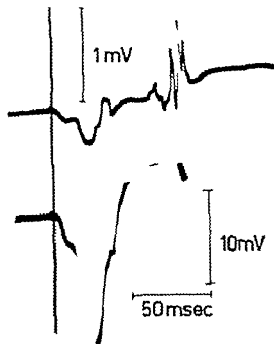


Fig 11 Differential complex (upper record) synchronous with unipolar complex (lower record) from one of the terminal of the differential electrode placed on the epicardial surface of a transmural infarction. The small deflections which occur 75 millisecond after the beginning of QRS are caused by excitation of tissue in contact with the differential electrode.

Chronic myocardial infarction

In 1934 an important paper by Wilson Johnston and Hill was published which forms the basis of much of our knowledge about the electrocardiographic changes in myocardial infarction.

Since the excitatory process spreads from the endocardial surface to the outer layers it is difficult to see how it can reach the outer layers when the inner layers are dead or replaced by scar tissue. The aforementioned authors were unable to understand how the excitatory process can cross the infarcted tissue unless they supposed that this tissue is penetrated by living Purkinje fibers or by surviving strands of ordinary muscle.

With the methods outlined at the beginning of this lecture this important problem was tackled. *Epicardial and intramural* excitation patterns were investigated.

Epicardial excitation The epicardial excitation pattern in myocardial infarction was changed profoundly. The unipolar complexes showed definite abnormalities even if the infarction was situated in the subendocardial layers. Up until now we have not encountered a situation in which an infarction of the subendocardial region did not result in an abnormal epicardial complex. The major change in the QRS complex was the occurrence of abnormal

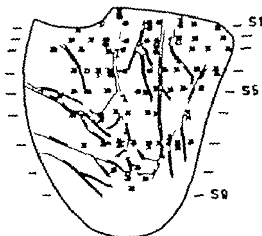


Fig 12 Activation time (msec) of epicardial surface in myocardial infarction. The epicardial surface above the subendocardial infarction, indicated by the dotted line is activated late in the cardiac cycle. In the region bordering the A V groove an area is activated with only slight delay (30 41 msec) and is lying close to an area activated much later (49 53 msec). Between these two areas fibrous tissue strands reach the epicardial surface acting as boundary for the crossing of the excitatory

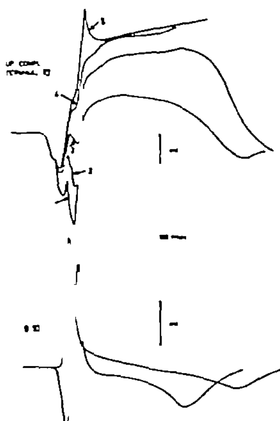


Fig 10 Changes in complexes during progressive coronary ischemia. Complex 1 was recorded 15 seconds after beginning of coronary occlusion complex 2 60 seconds complex 3 100 seconds complex 4 170 seconds complex 5 5 seconds after beginning of coronary occlusion. The arrows indicate the location of the intrinsic deflection. Bipolar complex 1 was registered synchronously with unipolar complex 1 complex 2 synchronously with unipolar complex 5. The downstroke of the R in unipolar complex 5 occurs synchronously with the downstroke in 9 10 and is caused by excitation of muscle layers in contact with terminal 10

other cases there was a loss of voltage in the bipolar complexes but this change was always associated with broadening of the bipolar complexes Fig 8 is a typical illustration The complexes are broad and show loss of voltage notching and S-T shift The broadening of these complexes is caused by a diminished conduction velocity of the excitatory process in the ischemic area—sometimes 10 cm per second or less The loss of voltage can possibly be related to a reduction of the membrane action potential The notching may be caused by the fact that the muscle fibers in the ischemic area are not changed to a similar degree by anoxia and do not conduct the excitatory process at the same rate

Sometimes and most frequently after the occlusion of a major branch or after prolonged occlusion of the coronary vessel complexes of a perplexing form are found (Fig 9 complex labeled *ischemia*) These bipolar complexes show a large reduction in voltage of the R and a large negative wave precedes the R Sometimes this R wave may disappear and the complex is completely negative

Bipolar complexes of this type may even be present in successive layers of the ventricular wall The changes which occur after restoration of blood supply may shed some light on the genesis of these complexes (Fig 9) It can be seen that the depth and duration of the negative wave diminish Simultaneously the positive deflection increases in voltage and also falls progressively earlier in the cardiac cycle After 20 to 30 seconds it is very high again and only a small negative wave precedes the positive deflection the complex has regained its preocclusion form It is an astonishing fact that the disappearance of the ischemic complexes occurs very rapidly mostly within one half to one minute after the coronary circulation has been re-established During that period multiple ventricular premature beats frequently occur Many experiments terminated in ventricular fibrillation during that period

It is possible that these bipolar complexes are caused by an increase in distance between sources and sinks of the polarized surface which represents the electrical effects of excitation

Changes in unipolar epicardial and intramural complexes During acute occlusion the form of the QRS complex of the unipolar epicardial complexes [1,17] and as we could prove also of the intramural complexes changes in the following manner (1) decrease in voltage of S sometimes even disappearance of the S (2) a gradual delay in the onset of the intrinsic deflection (3) decrease of the voltage and duration of the intrinsic deflection and (4) perhaps complete disappearance of the intrinsic deflection

Fig 10 depicts the changes in the form of the unipolar intramural complex during coronary occlusion The intrinsic deflection demonstrates the changes just described

deflections. Therefore the deflections in the unipolar complex are caused by local excitation of the subepicardial muscle layers. This excitation occurs late in the cardiac cycle (75 to 80 milliseconds) at the moment at which depolarization of the remainder of the heart is completed and even repolarization in a large part of the ventricles is taking place. The pathway of excitation in this area of a few square millimeters is very bizarre but neverthe less the pathway is constant from beat to beat. No variations however small are allowed: the pathway of excitation is strictly determined.

The form of the differential complexes shows that even in that small area large desynchronization of excitation occurs: the excitatory wave is highly fragmented.

Time relations of the epicardial surface. Analysis of the time relations of epicardial break through above a subendocardial in farction reveals some interesting facts. In most of the cases it occurs late in the cardiac cycle (Fig. 12).

An accurate analysis of epicardial exci tation reveals that areas lying very close together may show great differences in times of arrival of the excitatory wave. In this case an offshoot of fibrous tissue from the subendocardial infarction reached the epicardial surface and acted as a barrier for the crossing of the excitatory process from the region activated early toward the neighboring region activated late in the cardiac cycle.

Bipolar intramural complexes (Fig. 13). The form of the bipolar complexes in the intramural leads was changed: (1) The voltage was reduced; sometimes a large reduction of voltage was present. (2) The complexes showed broadening and multi ple notching.

They may become polyphasic. Small fast deflections are nearly always present. In our opinion these small deflections are caused by successive excitation of strands of muscle fibers in contact with the ex ploring terminals. During subepicardial stimulation the polarity of the bipolar complexes points to the presence of a highly fragmented excitatory wave pro gressing in an endocardial direction.

Intramural time relations. A gradual mopping up process of the intrainfarc tion muscle fibers takes place. It takes a long time before all of the intrainfarction muscle fibers are depolarized. The excita tory waves take devious routes but they are constant from beat to beat.

Wilson in the paper already cited wrote that it was the hope of himself and his colleagues that studies of the refractory period in the infarcted region would yield important information in regard to the ability of the affected muscle to respond to the excitatory process.

We measured the excitability of intra infarction muscle fibers (Fig. 14). There appeared to be no large change for cathodal and anodal excitability compared to nor mal ventricular muscles. Sometimes the diastolic threshold was somewhat higher than in normal muscle, perhaps due to short circuiting by nonexcitable tissue.

How does the excitatory wave reach the muscle fibers in the infarcted area? We looked for evidence of Purkinje activity in the subendocardial tissue but could only demonstrate it in a few cases. In most of these cases Purkinje activation occurred at a normal time at the beginning of the left ventricular cavitary potential. No delay in activation of the subendocardial Purkinje fibers could be demonstrated. In

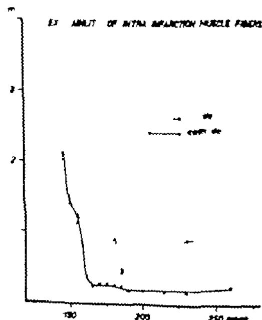


Fig. 14. Excitability of [illegible] muscle fibers lying in a 6-week-old infarction. The excitability of [illegible] surviving muscle fibers is nearly normal.

only one case were subendocardial Purkinje fibers activated relatively late in the cardiac cycle

Because of the tangential excitation which may take place in the outer layers above the infarcted area the Q R relation does not nece arily give evi l nce about the degree of intramural extension of a subendocardial infarction

The Q in ubendocardial myocardial infarction is caused mainly by the reduction in voltage generated during activation of these regions In only one case could we find evidence of a delay in transmission of the excitatory process from the Purkinje fibers to the muscle fibers

Closing remarks

Mr Chairman looking back to what has been achieved with the methods given to the world by the man whose birthday we commemorate today we are deeply impressed by the great amount of work that has been done But looking forward we feel humble because there is still so much to do One point is very important The bridge separating electrocardiography as a part of physiology from electrocardiography as a part of clinical medicine has been bridged by workers in both fields physiologists working in one direction clinicians in the other one They can at last understand what the other party is doing because more or less they have learned to speak a common language

REFERENCES

1 L Zbyszewski Beobacht ngen uber die Erregung des isolierten Herzens Arb d physiol Institut der Univer tat Lemberg
2 Boden E nd Neukirch P Elektrokardiographische Studien am isolierten Säugetier und Menschenherzen bei direkt nd indirekter Ableit ng Pflüger Arch 1 1 147 1918
3 Durrer D and Van der Tweel L H Excitation of the left entricular wall of the dog nd goat Ann New York Acad Sc 65 779 1957
4 Durrer D nd V der Tweel L H Spread of activ tion in the left entricular wall of the dog II Am Heart J 4 192 1954
5 Scher A M and Young A C Ventricular depolarization nd the gene of QRS Ann New York Acad Sc 65 768 1957
6 Sodi P llares D and Calder R M New bases of electrocard raphy St Louis 1956 The C V Mosby Company
7 Pruitt R D E sex H E and Burchell H B Studies on the spread of excit tion through the vent icular myocardium Circulation 3 418 1951
8 Meyl r H A nd Ter Borg H The conduct ng s tem of the heart a hoofed animal Cornell Veterinarian 1 419 1937
9 Ter Borg H The transventricul conduction s t m of the big domestic animals and more especially on the terminal ramificati n of the Purkinje fibers and the so-called interventricular connection Act neerl morphol 1 97 1941
10 Scher A M Young A C Malmgren A C and Erickson R V Activ tion of the interventricular septum Circulation I es 3 56 1955
11 Burchell H B E sex H E nd Pruitt R D Studies on the prea l of excitation through the ent icul myocardium II The entricular septum Circul t on 6 161 1952
12 Medrano C A Bisteni A Brancato R W Pileggi F nd Sodi P ll res D The activation of the interventricul septum in the dog be rt under normal con lit ons and in l undle branch block Ann New York Acad Sc 65 804 1957
13 V Dam R Th Over het prikkelbaa heids erl op an de hart pier These Amsterdam 1960
14 Durrer D Büller H Graaff P Lo C I nd Meyler F L The excit tion of the isol ted rev ed huma fetal heart Circulation Res (T be publ hed)
15 Lewis Th The mech nism and graphic registration of the heartbeat London 1925 Sh w nd Sons Ltd p 115
16 Wilson F N Johnston F D nd Hill I G W The interpretation of the galvanometric curves obtained when one electrode is d tant from the heart and the other nea or in contact with the ventricul r urface Part II Observations on the mammal an heart Am Heart J 10 1 6 1934
17 Johnston F D Hill I G W and Wilson F N The form of the lectrocardiogram in expe iment l myocardial nfarction II The early effect produced by ligation of the a terior descending branch of the left coronary artery Am Heart J 10 889 1935
18 Wilson F N Joh ton F D and Hill I G W The form of the electrocardiogram in experimental myocardial infarction IV Addi tional observations on the later effects produced by ligation of the terior descending branch f the left coronary artery Am Heart J 10 1025 1935

Discussion

W. Trautwein (Heidelberg, Germany): Before the beginning of the general discussion I shall try to add some information which concerns automaticity and the effects of vagal and sympathetic stimulation on heart muscle fibers. At first I should like to mention the differences in the cyclic membrane potential changes between fibers spontaneously active and those which do not beat spontaneously. Whereas in the ventricular and atrial fibers which are excited by conduction the diastolic membrane potential remains constant, the fibers of the sinus and Purkinje system show a spontaneous slow depolarization to threshold in diastole (see Fig. 1). Within the sinus the rate of this slow diastolic depolarization is greatest at the focus of the pacemaker. A few millimeters apart from it the fiber is excited by conduction. The analysis of the mechanism underlying spontaneity is not yet complete, but it may be said that there is evidence of a higher resting sodium permeability in spontaneously beating fibers than in the nonspontaneously beating ones.

Fig. 1 *B* shows the effects of vagal stimulation on the membrane potential of a spontaneously beating frog sinus fiber presumably taken at the pacemaker. Again there is a slow diastolic depolarization which progresses smoothly into the steep rise of the action potential. The peaks of the action potentials are cut off and cannot be seen on the record. The vagus was stimulated at a rate of 10 shocks per second during the interruption of the reference line. The pacemaker potential is immediately suppressed and the maximal diastolic potential increases. The upper tracing (Fig. 1,*A*) shows the effects of acetylcholine on the membrane potential of a spontaneously beating dog sinus fiber. The arrow indicates the application of acetylcholine which immediately causes a suppression of the pacemaker potential. After two beats which arise in the deeper part of the preparation and are conducted to the impaled superficial fiber, the preparation is arrested. The two main features of the inhibition shown in this figure are the arrest of the heartbeat and the hyperpolarization. The well known shortening of the duration of the action potential can also be seen.

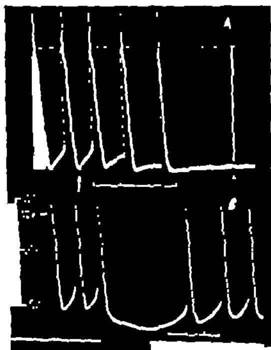


Fig. 1. *A*, Spontaneously beating dog sinus fiber. The arrow indicates application of acetylcholine. Note the suppression of the pacemaker potential and the slight hyperpolarization. The third to fifth action potentials are conducted responses. Ordinate 20 mV; abscissa second (from Trautwein, Physiologie der Herzirregularitäten. *In* Spang, Die unregelmässige Herztätigkeit. Stuttgart, 1957). *B*, Spontaneously beating frog sinus fiber. The vagus was stimulated at rate of 20 per second during interruption of the reference line. Abscissa second (from Hutter and Trautwein, J. Gen. Physiol. 39: 715, 1956).

Physiologisches Institut, Extraordinariat f. Physiologie d. [illegible], Germany.



Fig. 2. Effect of sympathetic stimulation on the slope of the pacemaker potential and the amplitude of the action potential. Stimulation of the vago-sympathetic trunk (atropinized preparation) at a rate of 20 per second during the interruption of the reference line. (From Hutter and Trautwein: J. Gen. Physiol. 39:715, 1956.)

The mechanism of vagal inhibition has been extensively studied both by electrophysiologic and radioisotope techniques. The experimental evidence fits perfectly well into the concept of ionic theory of excitation in heart muscle which Dr. Weidmann presented. It supports the view that acetylcholine acts by specifically increasing the membrane conductance for potassium. Such a mode of action explains the phenomenon which I have just described. For instance, the hyperpolarization and suppression of the pacemaker potential are the result of the rapid increase in potassium permeability by which the membrane potential is driven toward the potassium equilibrium potential, thus stabilizing the membrane at a high membrane potential. Moreover, the shortening of the action potential by acetylcholine or by vagal stimulation is due to the specific increase in potassium permeability; increases the efficiency of the driving force during the plateau. Thus, the normal repolarization is accelerated by an additional increase in the permeability to the repolarizing ion.

Although the inhibitory effect of acetylcholine is quite well understood as an increase in the passive potassium permeability, an explanation of the effect of the sympathetic stimulation or adrenaline is more difficult. Fig. 2 shows the effect of the sympathetic stimulation on an innervated excised sinus venosus of the frog heart. During the interruption of the reference line the sympathetic trunk was stimulated. This caused the rate of the slow depolarization to increase progressively, thus increasing the frequency of the sinus while the threshold remained nearly constant. At the same time the overshoot and the rate of rise increased. A slight rise in membrane potential clearly accounts for this latter effect on corresponding mammalian tissue. The loss of plateau in a hypodynamic or metabolically inhibited fiber is mostly counteracted by adrenaline, and the duration of the action potential may be prolonged to control values. All evidence we have favors the assumption that adrenaline does not act by changing passive permeabilities of the fiber membrane but rather by increasing the activity of a metabolically driven ion pump. This brings us back to Dr. Weidmann's analysis of the events during the plateau. I should like to open the general discussion with the question: Should we assume that active ion transport affects the time course of the action potential exclusively by controlling the extracellular potassium and/or intracellular sodium concentration, or is it perhaps possible that the pump moves a net charge which produces a change in membrane potential.

S. WEIDMANN, Bern, Switzerland: In my opinion there is no conclusive evidence to show that active transport contributes to the time course of the action potential in the sense that the rate of pumping for certain ions changes in the course of one cardiac cycle. One might put forward the hypothesis that a net inflow of potassium ions during the plateau phase is responsible for the long lasting action potential which is typical for cardiac tissue. The shortening of the action potential observed with metabolic poisons would then find an easy explanation. Also it had been suggested that repolarization might be due to active transport of sodium ions from inside out. But again I should like to stress that there is not enough evidence to place too much weight on such a hypothesis.

Heart vector and leads

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The investigation of the electrical action of the heart without serious intervention in the life processes must in practice be based on measurements of potential on the body surface The development of research has followed two entirely different paths The first one is the collection of empirical data concerning the relation between heart disease and the electrocardiograms taken from the periphery and is the method of conventional electrocardiography the importance of which I need not emphasize Neither do I need to stress the great merit of Einthoven in this connection But Einthoven led the way to another approach to this problem in originating the notion of what is now called the heart vector He drew attention to an interpretation of the ECG as a consequence of a series of events beginning with an electrical action inside the heart muscle This electrical action sets up a field of current in the trunk and this in its turn generates a distribution of potential over the body surface (Fig 1) This connection of inside action and outside effect represents a physical problem and this may explain why a physicist has the honor of speaking to you on this occasion

It is noteworthy that Einthoven tackled the subject geometrically His triangle (Fig 2) is too well known to make it necessary to explain it here in detail But it is worth while to remark that this method is not only geometrical but also intuitive and naturally so The physical laws governing the field of current in a three-dimensional conductor such as the human trunk have an analytical form they are formulas And although they are partly expressed in the symbols of differential geometry the only possibility of drawing conclusions from them in a rational way is to solve a partial differential equation with boundary conditions

It must be said that the work of so many investigators after Einthoven has created a difficult situation Each of them has given his own idea concerning the relation between heart vector and leads and almost all of these systems are both geometrical and intuitive and therefore irrational I shall not mention names but it is my conviction that this variety of systems of vectorcardiography has hampered the development of vectorcardiography and that not only and not even mainly because they are not exact or not correct They give results that are appreciably different and therefore one investigator cannot interpret the results the patterns obtained according to the method of another Standardization is urgently needed and I think in this respect everybody agrees provided that the system he uses should be accepted as a standard To my mind there is only one way out of the present chaos and that is a rigorous study of the inside outside relation already mentioned It goes without saying that phy

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FIG. 2. Effect of sympathetic stimulation on the slope of the pacemaker potential and the amplitude of the action potential. Stimulation of the sympathetic trunk (atropinized preparation) at rate of 20 per second during the interruption of the reference line. (From Hutter and Trautwein: J. Gen. Physiol. 39:715, 1956.)

The mechanism of vagal inhibition has been extensively studied both by electrophysiologic and radioisotope techniques. The experimental evidence fits perfectly well into the concept of ionic theory of excitation in heart muscle which Dr. Weidmann presented. It supports the view that acetylcholine acts by specifically increasing the membrane conductance for potassium. Such a mode of action explains the phenomenon which I have just described. For instance, the hyperpolarization and suppression of the pacemaker potential are the result of the rapid increase in potassium permeability, by which the membrane potential is driven toward the potassium equilibrium potential, thus stabilizing the membrane at a high membrane potential. Moreover, the shortening of the action potential by acetylcholine or by vagal stimulation is due to the specific increase in potassium permeability; increases the efficiency of the driving force during the plateau. Thus, the normal repolarization is accelerated by an additional increase in the permeability to the repolarizing ion.

Although the inhibitory effect of acetylcholine is quite well understood as an increase in the passive potassium permeability, an explanation of the effect of the sympathetic stimulation or adrenaline is more difficult. Fig. 2 shows the effect of the sympathetic stimulation on an innervated excised sinus venosus of the frog heart. During the interruption of the reference line the sympathetic trunk was stimulated. This caused the rate of the slow depolarization to increase progressively, thus increasing the frequency of the sinus while the threshold remained nearly constant. At the same time the overshoot and the rate of rise increased. A slight rise in membrane potential clearly accounts for this latter effect on corresponding mammalian tissue. The loss of plateau in a hypodynamic or metabolically inhibited fiber is mostly counteracted by adrenaline and the duration of the action potential may be prolonged to control values. All evidence we have favors the assumption that adrenaline does not act by changing passive permeabilities of the fiber membrane but rather by increasing the activity of a metabolically driven ion pump. This brings us back to Dr. Weidmann's analysis of the events during the plateau. I should like to open the general discussion with the question: Should we assume that active ion transport affects the time course of the action potential exclusively by controlling the extracellular potassium and/or intracellular sodium concentration, or is it perhaps possible that the pump moves a net charge which produces a change in membrane potential?

S. WEIDMANN, Bern, Switzerland. In my opinion there is no conclusive evidence to show that active transport contributes to the time course of the action potential in the sense that the rate of pumping for certain ions changes in the course of one cardiac cycle. One might put forward the hypothesis that a net inflow of potassium ions during the plateau phase is responsible for the long lasting action potential which is typical for cardiac tissue. The shortening of the action potential observed with metabolic poisons would then find an easy explanation. Also it had been suggested that repolarization might be due to active transport of sodium ions from inside out. But again I should like to stress that there is not enough evidence to place too much weight on such a hypothesis.

coefficients abc on the other hand are constant i e independent of time It is by this equation that we express the linear relation of inside cause XYZ and outside result V

I shall remind you very briefly of how we can make practical use of this equation as the basis of a lead system of VCG From three equations of the type of the equation mentioned the three unknowns can be solved by elementary algebra To find the solution numerically the 3 × 3 coefficients must be known They can be determined by model experiments and it is here that points c and d of our list of conditions come in The shape of the body does not give serious difficulties and has seldom been the subject of discussion But d is a more important point Anisotropy has been neglected by all but I have reasons to doubt the justifiability of this neglect The opinion about heterogeneity seems to depend on nationality Whereas in this country we have reckoned with an appreciable heterogeneity the investigators in the United States have worked with a homogeneous model I suppose that the reality is intermediary and I hope that they believe so too

The numerical solution of the three equations gives the orthogonal components XYZ of the heart vector as a linear function of three independent leads By electronic means a display can be realized giving the heart vector and the vectorcardiogram in any projection These technical details do not belong to the subjects of this day

So far this analytical procedure does not need any geometrical means But if desired these can be deduced from our equation The latter can be interpreted as a relation between the scalar quantity V a voltage and two vectors the heart vector with orthogonal components XYZ and the so called lead vector with components a b c V is the so called scalar product of the two vectors XYZ and abc It is equal to the product of the magnitude of one of them and the projection of the other on this one This interpretation is secondary but popular among physicians It can be generalized by the conception of the image space in which every point of the body surface has its image

But let us leave this imaginary world to return to reality How can we check whether the assumptions with respect to b c and d are correct i e near enough to the truth to be the foundation of a clinical method? Of these assumptions b the dipole hypothesis is certainly the most essential one Is it a good approximation to assume that the dipole action is confined to a region the dimensions of which are small with respect to the corresponding dimensions of the thorax? There are two ways to answer this question

1 The first one in its most simple and at the same time most general form is a method indicated by the late Dr Becking It can be derived from the linear equation (1) From three equations of this type giving the voltage in three leads each expressed in the time functions XYZ the latter ones can be solved and expressed as linear functions of the three V's which are also time functions (electrocardiograms) Now these three linear functions of three V s can be substituted in a fourth equation of the same type valid for a fourth independent V In this way this fourth lead is expressed linearly in three other leads This must be true for any body independent of the position of the dipole if only it is point shaped (or at least very small) and stationary It is easy to test such a linear relation of four leads by electronic means but I will not explain to you here how it is done The result is that there are deviations from the ideal case great enough to be of practical importance It must be emphasized that these are measurements on human bodies They have nothing to do with model experiments or assumed coefficients They show in the most direct way that the dipole hypothesis although it has some meaning is a too fargoing simplification

Older than the Becking method but intimately related to it is the test of the dipole hypothesis that is known as the mirror image method or the cancellation method It is so well known that I shall not explain it here As to the result the opinions are not entirely unanimous Some investigators have stated their belief that according to this method it can be proved that the dipole is point shaped and stationary But I cannot help supposing t

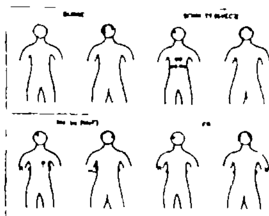


Fig. 3. Situation of the electrodes in the lead systems of Frank (F), Schmitt (S), McFee (M), and Burger (B).

some cases this is wishful thinking. In many cases, according to my own experience and that of others, the deviation from the pure dipole action is too great to be neglected. This is the more urgent since it is emphasized that a good cancellation may be arrived at with dipoles distributed over a volume that is not at all small with respect to the thorax.

2. A quite different test of the dipole hypothesis is a practical one: the comparison of loops obtained by different lead systems of VCG. By looking at the loops a subjective judgment of the correspondence is obtained, which has all the drawbacks of subjectivity, but at the same time all the advantages. But yet the comparison of loops obtained by different lead systems must be expressed in a quantitative way. Therefore we have awarded marks to the agreement, calling 10 the best agreement that can be expected, such as is shown by successive heartbeats in one and the same system. The correspondence of loops which show no relation at all is called zero. An advantage of these scores is that we can weigh the criteria according to their clinical significance, such as left or right preponderance and clockwise or counterclockwise rotation.

Long ago, when applying this method in comparing two systems of our own and a system without physical foundation, we found that the correspondence of those two was better than that of each of them with the third. But even when two systems based on model measurements are compared, the agreement in some cases is sometimes far from ideal. This cannot be ascribed to wrong coefficients alone. If this were so, the noncorrespondence should be of a simple kind, to be expressed by a linear transformation. This relation I hope to explain later. For the moment it may suffice to say that several investigators agree in the explanation of insufficient agreement in the majority of cases: the heart is not acting as a point shaped dipole but as a distribution of dipoles over the heart muscle. Since the latter is not small with respect to the dimensions of the trunk, the approximation of the dipole hypothesis is insufficient, especially for the sagittal component, i.e., the component in the direction of the smallest dimension of the human thorax.

Several investigators, and these are all physicists, have tried to take this circumstance into account. This problem could only be solved by applying an infinitely great number of electrodes, as was proved by Gabor and Nelson. But for practical reasons the number has to be restricted, and these are the arguments that count heavily for every physician applying vectorcardiography.

The correct way to investigate the influence of the dipole distribution over the heart, i.e., in a part of the thorax that is not at all small, is to use a model and move the artificial dipole in it. By experiments of this kind it is possible to study the effect of dipole position. Then an attempt can be made to design a system the lead of which will not depend too much on the dipole position, so that they can be used to find the total dipole irrespective of the distribution of its local constituents. This was carried out by some American investigators in a very elegant way. In our system we did it less sophisticatedly.

The old method of comparison, the award of scores, was the first one we applied to get an idea of the effectiveness of the use of more than the essential minimum number of electrodes, namely, four.

Lately, we have been comparing four systems, all with a sound physical foundation and corrected for dipole location. Three of them, all of American origin, are based on a homogeneous model. They are the systems of Frank, Schmitt (SVEC

III) and McFee. The McFee system was communicated to us by the author but has not yet been published as far as I know. The positions of the electrodes in the four systems are indicated in Fig. 3. The weights attached to the contributions of each electrode are effected by resistances as described in the publications of Frank and Schmitt. In McFee's system the two electrodes at the left side have the same weight just as is the case with the three precordial electrodes.

The fourth system is one of our own in which the quantitative relations were deduced from a heterogeneous model in which the specific resistance of the air filled lungs is taken to be four times that of average human tissue.

The number of electrodes of the systems compares as follows: homogeneous model—F 7 electrodes, S 14 electrodes, M 9 electrodes; heterogeneous model—B 5 electrodes.

This number is important for the decision of which system to use clinically, just as is the electrode location, especially that of the dorsal electrode or electrodes.

The result of the comparison is shown in Fig. 4. It has been deduced from some 150 to 200 comparisons, mainly cases of heart disease. The score is given for the agreement of the frontal and of the horizontal projections respectively. All combinations of the four systems figure in this diagram. The following conclusions can be drawn from it.

1. The agreement is better for the frontal than for the horizontal projection. This is a consequence of the uncertainty in the sagittal component of the heart vector caused by the small dimension of the human trunk in sagittal direction.

2. The agreement of the American lead systems F, S, and M *inter se* is better than that of B with each of these three. This may be caused by two circumstances: the small number of electrodes in B (5) that makes it more difficult to reduce the influence of dipole location, and the assumption of heterogeneity of the thorax in the B system.

3. The agreement between the S and M systems is so satisfactory that for practical purposes one of the two can be omitted. Since S has more electrodes than M, which is a complication in clinical use, we think that system S can be abandoned and M chosen in its place.

Only in a fraction of all cases does real discrepancy exist between any two systems, i.e., a difference so pronounced that it would lead to a different diagnosis. Anyhow, this fraction, of the order of 20 per cent for the worst combination of lead systems, is too great to be accepted.

In the last few months we have applied quite a different method of comparing lead systems. This procedure was tried tentatively some years ago but now we have used it more rigorously. We arrived at it by the following line of thought. If indeed the dipole hypothesis were true, then two arbitrary lead systems, each of them with any number of electrodes, should have a simple relation. From our fundamental equation

$$V = aX + bY + cZ$$

it can be deduced that each coordinate of a point of a loop in one of two arbitrary lead systems is a linear function of the coordinates in the other system. This is true whatever be the values of the coefficients chosen for the two systems; they may be correct or entirely wrong. The mathematical relation between two such lead systems (let us call them C and D) can be expressed by the following set of formulas:

$$\left.\begin{aligned} X_D &= p_1X + q_1Y + r_1Z \\ Y_D &= p_2X + q_2Y + r_2Z \\ Z_D &= p_3X + q_3Y + r_3Z \end{aligned}\right\} \quad (2)$$

I regret that I cannot describe this relation

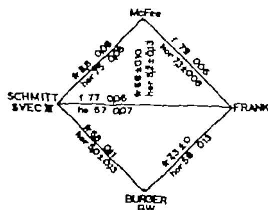


Fig. 4. Marks awarded to the agreement of vectorcardiograms. Averages and standard errors.

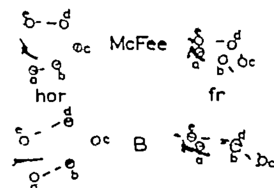


Fig. 5. Synchronous points a, b, ... d on frontal and horizontal projection of the vectorcardiogram ... lead system.

adequately without algebra but here again we have an example of the fact mentioned before that the algebraic form is primary. Yet it is possible to mention examples of linear relation or transformation that are expressed by a special form of this set of three linear equations and may be interpreted geometrically in a simple way. I refer to a rotation and a one sided or all sided dilatation or compression. Another transformation of this kind, less known in daily life but important in our problem, is a so called shear. In a special case it can be described geometrically as a horizontal displacement of all points to an extent proportional to the vertical coordinate. It is precisely this transformation that plays an important part when VCG systems are compared. This was evident from clinical discussions before it was demonstrated exactly by mathematical treatment.

I have hesitated a good deal before deciding to say more than a single word about this more exact mathematical treatment. I determined to do so because I prefer to be considered by you a bore rather than a mathematical witch doctor.

We can be certain a priori that the set of equations (2) does not hold generally because the dipole hypothesis is not generally true. So we have to reckon with the fact that (2) is a rough approximation only. It may be that in a single individual it describes tolerably well the relation of the loops in one lead system to those in another. But in another subject the nine coefficients p, q, r will have other values.

Now this is a practically worthless result. We are far from the ideal to adapt the lead system to the individual. What we need is a set of coefficients which are independent of the subject or patient. Therefore we must abandon the idea to allow for the accidental peculiarities of body build inside and outside and lay all subjects and patients in one and the same vectorcardiographic Procrustean bed. Apart from the individual and accidental varieties we may hope to find a systematic relation according to (2) between two lead systems when we compare the vectorcardiogram of a sufficient number of human bodies.

We never can find a set of nine coefficients (p, q ...) that satisfies the equations (2) for all points of the loops of all our subjects. But we must deduce the coefficients that are the best we can obtain. The practical solution is the following. On one pair of loops, frontal and horizontal, in one system for a certain individual we choose a number of corresponding points. Then we try to find the synchronous points on the frontal and horizontal projections of another system (Fig. 5). Each point, say a, has three coordinates that can be measured from the pair of projections in one system, say C, and likewise in the other, D. These 2 × 3 coordinates substituted in the equations (2) give three equations with the nine unknowns p, q, r. On each QRS loop we have chosen five points so that they determine its shape approximately. Since each pair of corresponding points gives three equations (2) for the nine unknowns these five points give 5 × 3 = 15 equations. So the number of equations (15) is more than the number of the unknowns (9), the problem is overdetermined. This is still the more true when we consider that there is no reason to restrict the calculation to one individual.

Therefore we have measured the coordinates of corresponding points on the loops of 150 or more subjects and solved these 150 × 15 equations with 9 unknowns. It is obvious that this is impossible in the ordinary algebraic sense. In such cases we try to make the best of it. We know that it is impossible to find nine coefficients p, q, r which satisfy these more than two thousand equations but we are con

tent with the nine values p, q, r that give the best, or the least bad, solution, a kind of average over all subjects. What this means exactly may be left unexplained here. May it suffice to say that the classic method of least squares gives a scheme for the calculation which is easy but tedious to perform. As an example, the average transformation of the Burger into the McFee system is given here:

$$\left.\begin{aligned} X_M &= 0.70\,X_B + 0.22\,Y_B + 0.23\,Z_B \\ Y_M &= 0.04\,X_B + 0.91\,Y_B - 0.16\,Z_B \\ Z_M &= -0.44\,X_B + 0.69\,Y_B + 1.11\,Z_B \end{aligned}\right\} \quad (3)$$

Such calculations make sense only when we draw conclusions from them and when these conclusions have any effect on our further behavior. The most important conclusion is that in addition to the systematic effect, as found in the way described above, there is a random effect caused by individual differences. In some individuals the average transformation fits quite well, so that, for example, after it is applied to a B loop it gives a loop that gives an excellent agreement with the M loop. But in other subjects the agreement after transformation is unsatisfactory. Yet the transformation is worth while since it reveals that the systematic discord expressed by it is of the same order as the random effects.

A second conclusion is that of all transformations that of S in M (or the reverse) is nearest to identity, thus confirming our subjective scores.

It would be well if the transformations could be expressed in a simple geometrical form. This cannot be done exactly, but as a first approximation B can be obtained from the other system by a shear. In the American system the downward part of the QRS loop is directed more to the back than in the B system.

We now have added a system that results from the B after transforming it to M. If there were no random individual effects and the dipole were point shaped, this new system would give results identical to those of the M system. In reality it does not agree so well, but yet the result of the transformation is not so bad. It gives a new B system—we call it B_M—which in the average agrees better with M than does the original B. The scores for the correspondence between B_M and M, as far as we have them now, are almost as good as those for the American systems mutually. Now, when we recognize that in B and B_M only five electrodes are used, this result is remarkably favorable.

What may be the cause of the systematic difference between B and the American systems? It is probable that, for a part at least, it is the assumed heterogeneity in the first system and the assumed homogeneity in the others. Model experiments with different amounts of heterogeneity and numbers of electrode positions in the four systems might contribute to the answer to this question.

The future of vectorcardiography depends on the degree of correspondence and noncorrespondence between different systems. What can we do about it? Can we standardize at this moment? I think one thing is certain: all systems without rational physical foundation must be abandoned. The correspondence among the remaining systems is not bad, even so that some cardiologists say that each of them can be used in clinical practice without serious discrepancies. I fear this is a little bit too optimistic. But in the transformation I described a way is shown for standardization, among others, by application of a transformation which provides a kind of average.

Let us be optimistic and suppose that in a few years a common opinion has been reached. What then? Is this the end of the task of the physicist in the development of vectorcardiography? I think not. All this was only hunting for the cardiac dipole. But then a much more elusive prey is left: the quadripole and further multipoles. And all of these must be seen as effects caused by the essential electrical processes of which Dr. Weidmann and Dr. Durrer have spoken. So I see a future of intimate collaboration of physicians or biologists with physicists in a time when there will be no longer a sharp boundary between these two groups of scientists.

Development in clinical electrocardiography since Einthoven

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The history of men of science reflects the history of science. Willem Einthoven, a humble, intelligent, and creative thinker, was a great man who was representative of the best in the history of medicine. Unfortunately, most of the history of medicine is a history of errors in a struggle for survival and self-aggrandizement. In the midst of such noncreative activity occasionally has come a man to advance knowledge and man himself. So it was with Einthoven. The full significance of great accomplishments is only partly realized at any one time, since the significance of great things grows endlessly. A creative development came with the sensitive, accurate, and reliable string galvanometer, a deliberate, methodical, and creative development from the brain of a great and modest man (Fig. 1). Modest and dedicated were even his associates. The early studies of electrocardiography in Einthoven's laboratory were of high quality. History of the subsequent developments in clinical electrocardiography outside Leiden reveals considerable variation in quality of investigations and reports and reflects more accurately the average state of clinical research and care of patients. As with the writings of great men, those of lesser men reflect and record for ever their personalities. May this continue, for then the true history of medicine is recorded, whatever it may be. To select and edit the works of man can only distort the work of man.

Perusal of reports in clinical electrocardiography reveals progress and development resembling that in other medical fields. Among the many contributors to the progress in electrocardiography were a few outstanding minds. Thomas Lewis, James Mackenzie, Alfred Cohn, H. F. Hollmann, W. Hollmann, K. F. Wenckebach, Frank Wilson, Ernest Starling, W. M. Bayliss, Carl Wiggers, Augustus Waller, James B. Herrick, Horatio B. Williams, W. H. Craib, H. C. Burger, and F. Schellong represent a few, in addition to Einthoven himself, who have been the stalwarts of research and development in clinical electrocardiography. Sir Thomas Lewis, who was most responsible for the early developments, was primarily interested in cardiac arrhythmias, whereas F. N. Wilson was the central figure of a slightly later electrocardiographic period who made extremely important contributions to other aspects of electrocardiography.

The history of the development of clini

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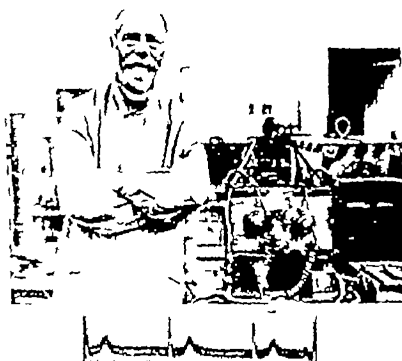


Fig 1 Willem Einthoven and his original galvanometer in his laboratory and a tracing obtained with the equipment (Reprinted courtesy of Cambridge Instrument Co)

cal electrocardiography may be divided into the following phases

1 The period prior to Einthoven during which time it was shown that electrical phenomena were associated with the heart beat Studies with the capillary electrometer revealed possible diagnostic alterations in the time course of electrical cardiac events associated with normal and abnormal cardiac states

2 The period of Einthoven which resulted in the development of the string galvanometer the contribution which made clinical electrocardiography possible (Figs 2 and 3)

3 The period of electrocardiographic study of disorders of the heart beat

4 The period in which coronary myocardial and nonarrhythmic disturbances of the heart were studied especially coronary heart disease

5 The period of the introduction of precordial and unipolar leads

6 Possibly the period of vectorcardiography

Prior to Einthoven's time important investigations in electrocardiography had been in progress The excellent work of Augustus Waller[4] and the previous studies of Helmholtz[4] in 1854 Kolliker and Muller[7] in 1856 Donders in 1872 Burdon Sanderson in 1880 and others have not been fully appreciated because of the overshadowing influence of Einthoven The capillary electrometer though insensitive difficult to employ and inaccurate displayed much information although it was not always recognized Its merits were appreciated by those well acquainted with the apparatus and its records This early work was little appreciated by fellow scientists who were poorly trained less interested or ill informed and who passed judgment without scientific justification or qualification Not until Einthoven's galvanometer became available did the value of this early work become obvious Einthoven's astonishingly excellent recordings were convincing

It was fully recognized by all r

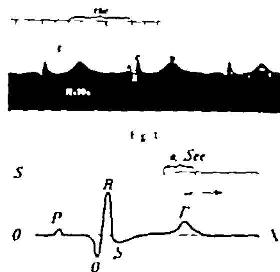


Fig. A recording obtained in 1903 with ... pillary electrometer and a constructed and corrected curve. The latter was ... tedious procedure before the string galvanometer. (Reprinted from Einthoven: Pflüger Arch ges Physiol 99:472, 1903.)

gists and the Nobel Committee in Medicine that it was the simple instrument of Einthoven and his clear description of certain theoretical electrocardiographic principles that made clinical and theoretical electrocardiography possible. Soon after the description of the galvanometer in 1903, Lewis obtained one and Cohn[11] brought the first electrocardiograph to the United States. Instruments were soon introduced in Germany, Austria, France, and other countries of the world. Interestingly, the first tracings published by Einthoven are still superior to most current recordings obtained by the direct writing method (Fig. 3).

Because of the great demand for his string galvanometer, Einthoven approached Horace Darwin, youngest son of the biologist and founder of the Cambridge Scientific Instrument Company, Ltd. of London, about the manufacture of his instrument. Darwin agreed and Einthoven worked as advisor to the company until his death in 1927.[12] The instrument was immediately simplified and made smaller. The first unit built by Cambridge was completed in 1911. By the outbreak of World War I, thirty-five had been supplied for clinical and research purposes.

The first electrocardiograph ever placed into operation in North America was an *Edelmann instrument made in Germany*, which Alfred Cohn brought to the U. S. A. with him for use at the Rockefeller Institute for Medical Research in the summer of 1909. This electrocardiograph is now in my laboratory at the Tulane Medical School (Fig. 4).

Cohn had spent the preceding spring and summer in the laboratory of Sir Thomas Lewis. The electrocardiograph installed in Lewis' laboratory at that time was also an Edelmann unit which had been purchased in 1908.

The first string galvanometer made in America was a type A ordered by Cohn in the fall of 1914. It was designed by Professor Horatio B. Williams and constructed by Charles F. Hindle, a mechanic in the workshop of the old College of Physicians and Surgeons, West Fifty-ninth Street, New York City. *This galvanometer* was delivered to Cohn at the beginning of May, 1915. The galvanometer for this electrocardiograph is now on display in the Smithsonian Institute in Washington, D. C. The first tracing obtained with the new type A galvanometer was recorded on May 20, 1915, on Mr. Joseph Webb.

The first paper published on electrocardiography in the United States was "The Electrocardiogram in Clinical Medicine" by Walter B. James and Horatio B. Williams, which appeared *in the American Journal of the Medical Sciences*, November, 1910.

It was in large measure because of the high standards of ethics in the manufacture, research, development, and marketing of these early machines that electrocardiography had such sound and successful growth. Functionally poor and unreliable production could have destroyed electrocardiography in its early days. The manufacturers have made and continue to make most significant contributions to electrocardiography (Fig. 5).

About 1928, Cassidy and Hall developed the first portable electrocardiograph. It weighed 80 pounds. In 1936, a portable instrument which weighed 30 pounds and used electronic methods was introduced. The first direct writer was introduced at Cambridge, England.

New portable apparatuses (Fig 6) have been developed and are now marketed at prices which make the electrocardiograph available to the individual doctor Then followed the direct writer portable electrocardiograph which is found in almost every doctor s office in the United States today With the increase in the number of electrocardiographs sold not only the use but also the abuse of electrocardiography has increased in clinical practice

Einthoven [1] made some of the important original clinical electrocardiographic observations (Fig 7) He noted that inspiration increased heart rate and that expiration decreased it He described the wave patterns in normal man the changes associated with respiration in the QRS complex in Lead III and the influence of cardiac position on the electrocardiogram He described the U wave in normal man published tracings of patients with left ventricular hypertrophy right ventricular hypertrophy subacute bacterial endocarditis myocardial degeneration and pericarditis Einthoven described the first electrocardiogram showing dextrocardia with situs inversus viscerum with and without the right and left arm electrodes reversed His classic report with Fahr and de Waart [6,7] on the principle and method for calculating the electrical axis at any time in the electrical cycle attests his interest in and knowledge of theoretical electrocardiography This method is still used to great advantage today in both clinical and experimental electrocardiography Einthoven and his associates demonstrated the use of the electrocardiogram for the timing of mechanical cardiac and pulsatile events [1] That the electrocardiogram played an early and major role in physiologic and clinical studies is probably due to Einthoven s early and intense in

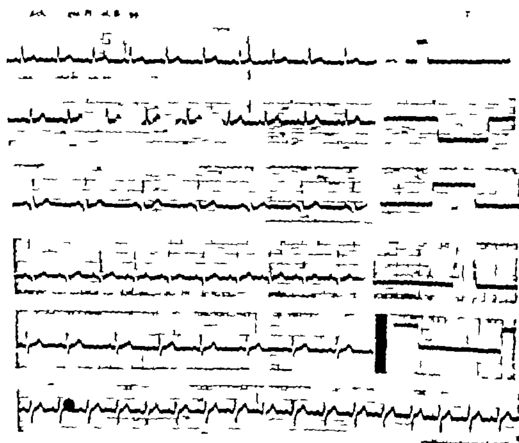


Fig 7 Several electrocardiograms obtained by Einthoven showing the excellence of the record obtained with his original electrocardiograph (Reprinted from Einthoven Pflüger Arch ges Phy siol 99 472 1903)

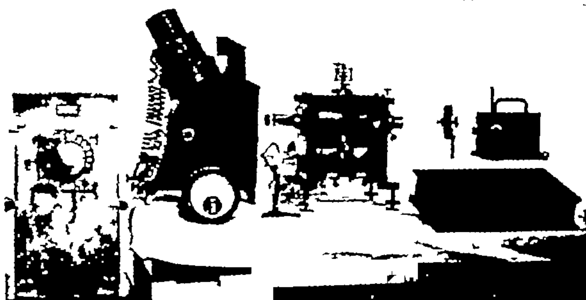


Fig. 7. The first Edelmann electrocardiograph used in the U.S.A. which was brought to this country by A. E. Cohn in 1909. It is now at the Tulane Medical School in New Orleans. The various parts of the electrocardiograph were placed on a table for this photograph.

terest in the clinical and practical applications of his apparatus, no doubt attributable in part to his own medical training as a doctor of medicine and to his father's experiences as a practicing physician.

Although Einthoven's clinical applications of the string galvanometer were relatively few compared to those of Sir Thomas Lewis of London, they were timely and of high quality. Einthoven was a physiologist and not a clinician. He recognized Lewis' contribution when he stated in his Nobel lecture that had it not been for Lewis' work he probably would not have received the Nobel prize because only a few people would have recognized his electrocardiograph as a useful clinical tool.

Lewis (Fig. 8) conducted an intensive, orderly, deliberate, and objective investigation of disorders of the heart beat. He established clinical investigation as sound research and showed the scientific world, as Mackenzie had done previously, that important fundamental research can be performed on man. Lewis worked with the Einthoven string galvanometer which was destined to record repeatedly discovery after discovery.[9,10] He worked in limited space under a stairway in the basement of the University College Hospital Medical School. He cleverly localized the site of the normal pacemaker of man and of dogs[7] by investigating the time course of the depolarization process in the heart of the dog and sharply localizing the point of origin of the impulse. The details of the time course of the depolarization process are a most important and still unsolved aspect of electrocardiography. This is under excellent investigation today by D. Durrer of Einthoven's country, Holland.[11,12]

It might be of interest to digress for a moment to illustrate the importance of the electrocardiograph of Einthoven in locating the sinoauricular node or pacemaker of the heart. The history of these studies shows the interrelationship of the interests, work, and methods of investigators in science which can result in important discoveries. For example, Martin Flack, as a young medical student at the London Hospital, visited his good friends, Dr. and Mrs. Arthur Keith, at their farm house, Mann's Place, near Bredgar in Kent,[13] during his summer vacation of 1906. The Keiths had converted their stud into a private laboratory which contained a collection of hearts from all sorts of wild and domestic animals of the area, and had plans to verify and extend

the significant discovery of the A V node by Tawara. One hot summer afternoon Dr and Mrs Keith decided to ride their bicycles and left Flack in the laboratory to cut serial sections of a paraffin embedded heart of a mole.

Upon their return Flack was in a state of excitement over the discovery of a strange mass of muscle like structure near the junction of the superior vena cava with the right atrium. It resembled the node of Tawara and was later shown by Keith and Flack to exist in the same place in the hearts of all of the other mammals. They assumed this to be the source of the cardiac rhythm of the heart.

In 1910 Lewis[20,22] *in brilliant experiments* with his new electrocardiograph showed in the dog that this special tissue remained *negative* to all depolarization processes of the atrium regardless of the direction of movement of the wave fronts which he recorded with his bipolar leads placed on the atria (Fig 9). The Oppenheimers then showed that this site of primary negativity was the special tissue described by Keith and Flack, thus identifying the node of Keith and Flack as the site of origin of the impulses of the heart beat.

As Lewis demonstrated, the galvanometer did not require much space and since the recordings were physically good, clear and permanent, well-designed experiments could be planned to answer important questions under relatively unfavorable working conditions. It was and still is possible to perform excellent clinical and experimental electrocardiographic research under a stairway if one is capable of asking the pertinent questions and designing the proper experiments. Lewis possessed the advantages of mental and physical vigor, a good electrocardiograph, curiosity, neatness and simplicity in experimental design and clear analytical thinking.

When Lewis began his studies in electrocardiography, Mackenzie was engaged in his classic work on cardiac irregularities using his relatively cumbersome and difficult polygraph. Lewis began his studies of cardiac irregularities using the Mackenzie type of polygraph. However, unlike Mackenzie, who was reluctant to accept *the electrocardiograph, Lewis quickly and* wisely recognized the electrocardiograph as a powerful tool especially suited for the study of cardiac irregularities. Although Mackenzie had established the importance of irregularities of the heart beat in clinical medicine, Lewis rapidly advanced and consolidated the state of knowledge. By means of the electrocardiograph he described the mechanism of important cardiac irregularities, defined the pathologic physiology, and established diagnostic and prognostic criteria, treatment and incidence[11,14,16,17] of the major disorders of the heart beat. He provided an excellent background for research by others so that the less common and more complicated irregularities could be readily recognized. New ones are still being described each year.

Lewis published about 100 lengthy detailed papers and three excellent monographs[7,15,16] on disorders of the heart beat

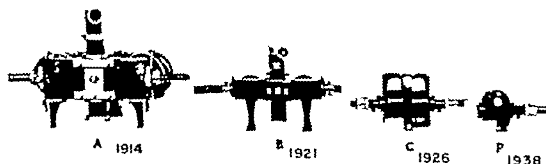


Fig 5 Progressive developments (1914 1938) in the string galvanometer showing the great reduction in size with successive model. (Reprinted courtesy of Cambridge Instrument Co.)

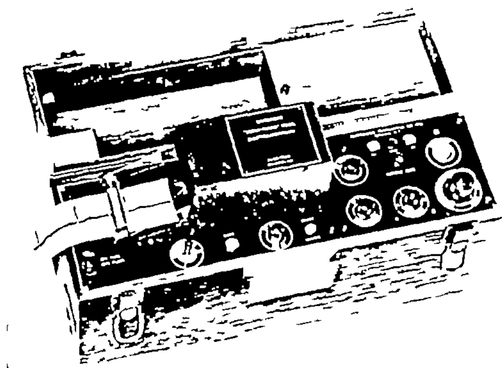


Fig. 6. The present-day model of the portable direct writer electrocardiograph. Compare with Fig. 1. (Reprinted courtesy of Cambridge Instrument Co.)

in which the electrocardiograph was shown to be the instrument par excellence. He bridged the period of the polygraph and the period of the electrocardiograph. His small book, *Clinical Disorders of the Heart Beat*,[16] should be read by every physician and certainly by anyone who undertakes to interpret electrocardiograms clinically. Lewis made very few mistakes in his great volumes of fine work. He was the first of the great clinical investigators to demonstrate to the biologists and basic scientists that excellent fundamental methodical research can be done on man, the highest of animals. Mackenzie and Lewis showed that man is a laboratory animal. It was Einthoven who made this possible. Few biologists have equaled Lewis in scientific accomplishment.

Lewis stated as early as 1912,[illegible] only nine years after Einthoven's original paper, that "the time is at hand, if it has not already come, when an examination of the heart is incomplete if this new method is neglected." It must have been a great satisfaction to Einthoven to see over 100 excellent papers appear from one man which demonstrated more and more the clinical importance and indispensability of his galvanometer. Lewis' book, *Mechanism and Graphic Registration of the Heart Beat*,[17] which appeared in 1920 and reached a third edition by 1925, summarized his work for the world and was the first great book on electrocardiography.

Lewis later shifted his interest from electrocardiography to clinical peripheral vascular physiology. With this change in research interest, the third era in clinical electrocardiography ended because there remained no one especially interested in an organized, orderly study of disorders of the heart beat. Many people subsequently have studied isolated problems of cardiac irregularities and have advanced the field, establishing electrocardiography even further as the best method for the study of cardiac irregularities. However, no one has yet equaled Lewis' scientific productivity in this field. Einthoven and Lewis must have been great friends and mutual scientific admirers.

The activities in electrocardiography during the first decade or two after the

description of the string galvanometer were concerned primarily with a few selected applications of the instrument. An important effort was that of educating clinicians, clinical investigators (a newly emerging type of investigator) and physiologists with the use of the electrocardiograph and its many advantages for the study of the time course of electrical events associated with the heart beat of man and other animals. The clinical applications of the electrocardiograph were then limited to a few centers; general clinical use came much later.

The fourth era in clinical electrocardiography began in 1912, when James B. Herrick [44] of Chicago clearly described the clinical syndrome of myocardial infarction and angina pectoris. He recorded an electrocardiogram on a patient with coronary disease and pointed out QRS and T wave changes associated with these diseases (Fig. 10). The normal patterns of the electrocardiogram were fairly well established by 1919, when Herrick [45] published his classic paper which vividly described the clinical syndrome of coronary occlusion and myocardial infarction so that people began to die of myocardial infarction rather than indigestion.

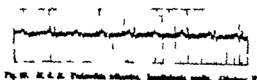


Fig. [illegible]

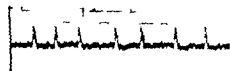


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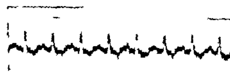


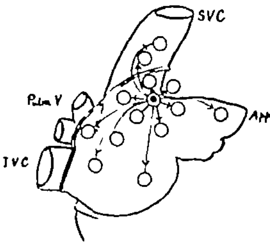
Fig. [illegible]

Fig. 7. Electrocardiograms for several diseases in man published by Einthoven in 1908. (Reprinted from Einthoven: Pflüger Arch. ges. Physiol. 122:517, 1908.)



Fig. 8. Sir Thomas Lewis. (Reprinted from Burch: *A Primer of Cardiology*. Philadelphia, 1933, Lea & Febiger.)

Herrick suggested to Fred Smith that he study the electrocardiographic and anatomic changes in the hearts of dogs after ligation of the coronary arteries.[46] Herrick, Smith and others established the electrocardiograph as a useful instrument for the study of cardiac disturbances other than disorders of the heart beat. Pardee[47, 48] described the coved or ischemic T wave, the Q-T pattern and other electrocardiographic changes associated with myocardial infarction. This aroused considerable interest in electrocardiography, especially when it became possible to recognize myocardial infarction and angina pectoris in the living patient. The electrocardiograph began to serve as the objective graphic method for establishing firmly and convincingly the clinical diagnosis of coronary heart disease. Those who had considered the electrocardiograph to be merely an improvement over the polygraph for the diagnosis of irregularities in cardiac rhythm and not otherwise an especially important clinical instrument began to realize that it recorded important phenomena which the polygraph was incap-



The contact [illegible] The central [illegible] which [illegible] ty in the [illegible] overlies the S-A node

Fig 9 Diagram from Lewis paper showing his localization of the site of the S-A node in the dog by means of the electrocardiograph (Reprinted from Lewis *Lectures on the Heart* New York 1915 Paul B Hoeber)

able of detecting This new application excited the curiosity of many and convinced even the skeptics that the electrocardiograph had far reaching potentialities in clinical medicine

Bousfield[44] in 1918 initiated clinical interest in the electrocardiographic changes in angina pectoris with the publication of the first tracing recorded during an attack of angina pectoris (Fig 11) Ten years later Feil and Siegel[45] recorded the electrocardiogram on patients during attacks of angina pectoris (Fig 12) and showed S T segment and T wave changes during the episode of pain These observations were quickly repeated and elaborated upon by others so that the electrocardiogram was soon shown to be useful in the diagnosis and management of angina pectoris Feil demonstrated his tracings to Sir Thomas Lewis when the latter was lecturing in the United States[41] and aroused Lewis interest

The electrocardiogram was studied further both clinically and experimentally[47] [illegible] in order to learn more of its value in coronary artery disease It was shown to be useful in following in detail the progress of healing of infarcts as well as important subtle subclinical changes in ischemic heart disease

Master and Oppenheimer[70] introduced the two step test as a procedure for measuring mechanical cardiac efficiency Master wrote on this phase of the test for a number of years before he suggested its use as a method to precipitate attacks of angina pectoris and the associated diagnostic electrocardiographic changes [illegible] Levy[44] introduced the anoxia test for the same purpose These tests extended further the clinical applications of electrocardiography

Lewis[illegible] had recorded the electrocardiogram with electrodes placed directly upon the epicardium Wilson had also been interested in similar studies [illegible] Neither however had shown the clinical usefulness of leads obtained with electrodes placed over the precordium or elsewhere on the surface of the chest Nevertheless their experiments initiated the next era in clinical electrocardiography It was Wolferth and Wood who first effectively and convincingly demonstrated the clinical value of the precordial lead in the diagnosis of myocardial infarction [illegible] They introduced a new lead the apical or fourth lead to clinical cardiology The clinical value of this lead was so well established by these investigators that when their paper appeared many other clinicians immediately began to repeat these studies and to introduce chest leads of their own Reports began to appear at such a rapid rate with so many different reasonable and unreasonable suggestions for recording the special leads that only a few physicians were able to follow the ideas This led to such confusion that a special committee was appointed by the American Heart Association and the Cardiac Society of Great Britain and Ireland to standardize the chest leads The committee's recommendations in 1938[9] immediately halted the confusion It is interesting to note however that as with many committee decisions the recommendations were so much influenced by prejudices and subjective factors of the time that all members of the committee except one failed to recognize the importance of the central terminal of Wilson and his unipolar lead concept[illegible] which were already strongly taking root in many of the better electro

cardiographic laboratories The superiority of this lead system is evident from its general use today In time accomplishments eventually reach their proper level This one achieved its level quickly and within the lifetime of the members of the special committee

With the advent of multiple precordial leads unipolar limb leads and augmented unipolar limb leads[illegible] clinical electrocardiography entered its fifth era These new leads are useful not only in the diagnosis and management of cardiac irregularities but also in the diagnosis and management of diseases of the myocardium pericardium and endocardium as well as of diseases of the aorta and noncardiac organs which indirectly disturb the heart The augmented unipolar limb lead[illegible] has its value in making simple the construction of a selector switch for the present day electrocardiographs

It would be impossible to discuss all of the numerous advances in clinical electrocardiography which resulted from the use of precordial leads[illegible] Precordial leads are an indispensable part of conventional clinical electrocardiography

During the third fourth fifth and early sixth decades of this century important advancements were made in theoretical electrocardiography[illegible] and in training and education in the field Wilson and his associates published many important papers[illegible] which clarified existing concepts in electrocardiography and introduced new ones Wilson introduced the concept of the ventricular gradient[illegible] one of his most important contributions (Fig 13) This concept was developed by Ashman[illegible] and its clinical usefulness was extended by other investigators Unfortunately the ventricular gradient has not yet received the attention it deserves It will when satisfactory integrating circuits are developed to eliminate the tedious manual calculations presently obtained from conventionally recorded electrocardiograms

It was not until 1932[illegible] that the electrocardiographic patterns for the diagnosis and differentiation of right and left bundle branch block were clarified in studies in dogs by Wilson Macleod and Barker They and others showed with theoretical and pathologic[illegible] data that the presently ac

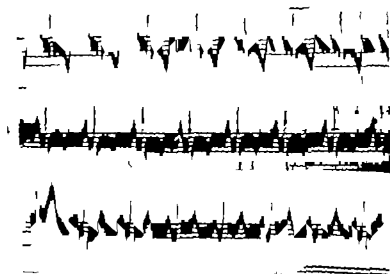


Fig *10* Tracings published in 1919 by James B Herrick in his classic paper describing the clinical syndrome of coronary occlusion (Reprinted from Herrick J A M A 72 387 1919)

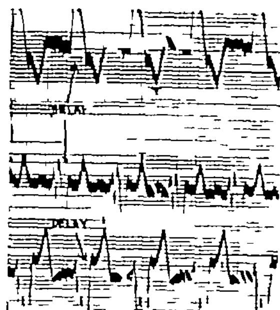


Fig. 13. The first published tracings on a patient with angina pectoris. (Reprinted from Bousfield: Lancet 1:457, 1918.)

cepted diagnostic electrocardiographic criteria are correct for complete bundle branch block. It may be added parenthetically that there are still many unsolved problems in the field of disturbances in conduction.

Recently there has been a significant and rewarding entrance of physicists, biophysicists, engineers, and mathematicians into the field of experimental and theoretical electrocardiography. Professor H. C. Burger, like Einthoven a Dutchman, has made and is still making important fundamental advances in electrocardiography.[124, 125] His lucid, concise, modest, and important contributions have received the recognition of all investigators in electrocardiography. These are appreciated by all who are engaged in a serious study of electrocardiography.

Hubert Mann[131, 132] of New York introduced the concept of the monocardiogram (Fig. 14) in 1920 and reported on the subject on several occasions. He even introduced a special mirror galvanometer activated by three electromagnetic coils[133] to record the monocardiogram mechanically. His work was ignored for about 15 years until Wilson and his associates,[134, 136] Schellong[138, 139] (Fig. 15), and Hollmann and Hollmann[140, 141] independently and essentially simultaneously introduced the cathode ray oscilloscope to record the monocardiogram which they independently renamed the vectorcardiogram.

During World War II only a few investigators[142, 143] studied the vectorcardiogram. Once the war was over, interest in the field of vectorcardiography increased. A considerable number of papers on the subject followed.[144-147] As with the precordial leads a decade before, opinions varied widely concerning the technique and electrode placement in and clinical significance of spatial vectorcardiography.[148] This discordance has impaired the clinical but not necessarily the scientific development of vectorcardiography. With continued study and more extensive clinical use of spatial vectorcardiography, its clinical possibilities are becoming established. Although it will not replace conventional clinical electrocardiography, it does supplement it. Once fully established as clinically useful, the adoption of vectorcardiography will establish the sixth era of clinical electrocardiography. This era has not yet arrived.

The present rapid development of computer analysis of clinical data includes electronic interpretation of electrocardiographic data. This may eliminate some of the gross errors in the interpretation of electrocardiograms made by ill-informed clinicians. Although appearing complicated at first glance, the use of electronic computers in electrocardiographic interpretations need and is receiving diligent study today.

With man's penetration into space and the associated advances in telemetering physiologic data over great distances, the electrocardiograph has entered a new field of research and application. When the United States Army's Research Division sent the two monkeys 300 miles into space and back safely, the electrocardiograph was used to record during flight every heart beat and to follow in minute detail the behavior of the two hearts.[149] Electrocardiography continues to spread into new fields of study.

It is impossible to emphasize adequately the developments and contributions of each person to clinical electrocardiography. Lewis' book[27] summarizes the important work up to 1925. Other monographs[150, 151]

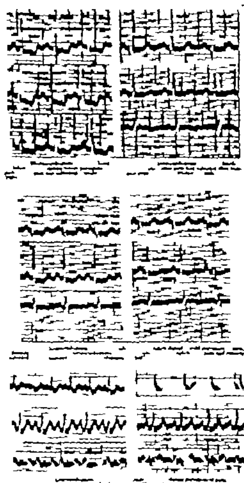


Fig 12. One of the first published electrocardiograms obtained on patient during an episode of anginal pain (Reprinted from Feil and Siegel Am J M Sc 175 255 1928)

and reviews[81] indicate advances since that period Reference must be made to these publications in order to appreciate the importance of the many developments and the work of the many contributors Furthermore electrocardiography has been applied to many clinical states and new ones appear regularly Newer clinical applications include a study of electrocardiographic changes produced by disturbances in electrolyte metabolism lesions of the central nervous system alcoholism metabolic disturbances and others too numerous to mention

The electrocardiogram and electrical cardiac events have been extremely useful in other clinical problems such as the timing of murmurs and mechanical events of the heart beat (Fig 16) and the precise triggering of apparatus[82] The electrocardiogram has been used to monitor the heart during cardiac catheterization pericardiocentesis anesthesia cardiac surgery quinidine therapy electrolyte therapy treatment of systemic medical emergencies and physiologic and pharmacologic experiments No clinical center or physiologic laboratory of any importance is without access to an electrocardiograph and many have several including multichannel recorders in everyday use for clinical or research purposes or both

The clinical developments in electrocardiography illustrate the historical developments in any clinical procedure The major development of Einthoven the string galvanometer was described in 1903 Its importance was realized by only a few investigators who immediately began to exploit its possibilities to answer important questions Other investigators seemed to have resisted the electrocardiograph probably because their course of investigations of the heart had suddenly become archaic Most people were not even aware of Ein

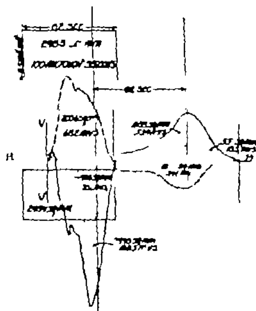


Fig 13 An illustration obtained from the original and classic paper by Wilson and associates on the ventricular gradient Tracings of ventricular complexes Area measurements were made with a planimeter (Reprinted from Wilson et al Am Heart J 10 46 1934)

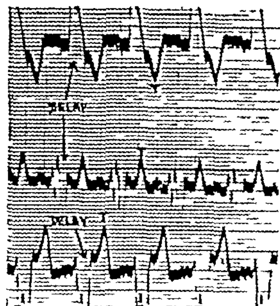


Fig. 13. The first published tracings on a patient with angina pectoris. (Reprinted from Bousfield: Lancet [illegible] 457, 1918.)

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Had a complicated reference system been introduced clinical electrocardiography would have been retarded Anyway no reference frame can be perfect Arrighi [137, 138] in 1939 introduced a different and interesting reference frame but this could not be expected to replace the simple reliable and reproducible one used today throughout the world

Wilson and his associates and students were the first after Einthoven made his initial theoretical investigations [4] to study methodically the theoretical aspects of electrocardiography [60] Although not strictly clinical in nature these studies placed electrocardiography on a sound foundation and were responsible for important clinical advancements There has been an increase in interest in the last 10 years in this type of theoretical physical and mathematical approach to problems in electrocardiography with more physicists engineers biophysicists and mathematicians working in the field than ever before These investigations have assisted the clinical applications

An important nonclinical electrocardiographic advancement which has influenced and will continue to influence clinical concepts in electrocardiography was made by Woodbury and Woodbury [139] when they introduced a very simple microelectrode technique for the study of the time course of variations in membrane potential of a single fiber of mammalian heart muscle Weidmann of Switzerland and Brooks in the United States have been making especially important contributions in this field These studies have had considerable influence upon clinical electrocardiography

Within recent years there has been greater interest among the more sophisticated university heart stations in the electrophysiologic explanation for the alterations produced by cardiac disease Schellong [140] illustrated very nicely the application of the concept of monophasic action current to an explanation of the effects of digitalis on the T wave and the T wave changes due to myocardial disease Theoretical and experimental investigations have become an essential part of the routine operation of the heart stations of

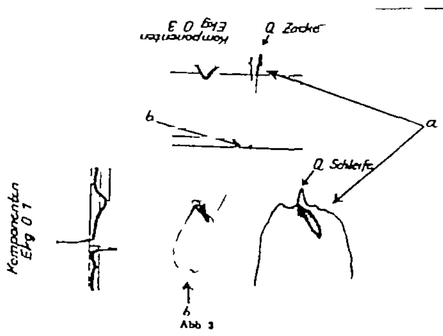


Fig 13 A ectorcard ogram recorded by means of the cathode ray oscilloscope rela tively new electronic device in 1937 Wilson [144] Hollmann and Hollmann [??] and Schellong [??] published the same idea almost simultaneously (Reprinted from Schellong Ztschr Kreislaufforsch 29 498 1937)

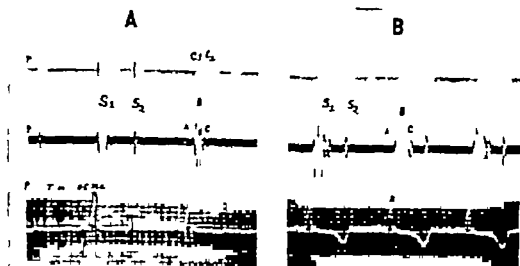


Fig 4 Record showing aortic sounds (upper curve), right ventricular sounds (middle curve) and relation to EKG, lead II A, during hypodynamic heart action consequent to opening chest, B, during action of adrenalin (one-half actual size)

Fig 16 Illustration showing early use of the electrocardiogram to time cardiovascular mechanical and hemodynamic phenomena (Reprinted from Wiggers and Dean Am J Physiol 42 476 1917)

medical schools and university hospitals Through the efforts of many workers the electrocardiogram was studied in experimental animals and in normal and diseased man and was correlated with clinical and autopsy data with the ultimate objective of developing its clinical application to the maintenance of the health and happiness of man Its clinical usefulness is fully established today probably far more extensively than once thought possible by Einthoven and the early workers

With the clinical use of the electrocardiograph at the bedside of patients and in the offices of doctors all over the world interesting behavior in cardiac mechanism and electrical phenomena under various circumstances of cardiac disease and therapy have been recorded Ventricular fibrillation ventricular tachycardia complete heart block conduction defects the behavior of the heart in dying people in anesthetized people in patients in severe circulatory collapse in cardiac pain in cardiac tamponade before during and after pericardial paracentesis in exercise fainting attacks of angina pectoris coma operations defibrillation and in many other clinical and physiologic conditions and circumstances have been observed electrocardiographically

It is not always possible to ascertain accurately when the descriptions of specific electrocardiographic observations were first published For example the first published recording of ventricular fibrillation in a patient who survived is shown in Fig 17 It is interesting to note that Einthoven published some of the first electrocardiograms in various types of cardiac disease Cremer[63] in 1906 apparently was the first to record simultaneously an electrocardiogram of the fetus and the mother (Fig 18) Incidentally the obstetrical applications of electrocardiography have not been fully developed

Wilson and associates[74] were the first to show that filling the stomach with cold water lowered the T wave in the electrocardiogram This report as well as those from other laboratories emphasized the importance of considering the marked vari

ations that can occur in the electrocardiogram of a normal person when he is subjected to relatively minor environmental stress. These factors are always considered in good electrocardiographic laboratories.

The practicing physician was assisted in the clinical developments in electrocardiography by the physiologist although mainly by a relatively new kind of clinician, the clinical investigator. It was the latter who made the greatest contributions and major advances in electrocardiography since Einthoven. Electrocardiograms were published early for the goldfish, frog, tortoise, and pigeon (Fig. 19), for the dog with and without chloroform and with and without intact vagi, for the snail's heart with and without $CaCl_2$, of the first beats of the chick embryo,[144] and for many other animals and circumstances. These early recordings were most important because they clearly demonstrated the wide range of applicability of the Einthoven galvanometer in research and its great potential for the study of normal and diseased heart. Experimental studies on animals provided a better understanding of electrocardiographic problems in man.

The course of the development of clinical electrocardiography was not a smooth one. It had to progress within an environment created by man. The prejudices and selfishness of men actively and passively obstructed its path. The greatest interference originated from those with the least knowledge of the subject and from those who were strongly opinionated. For example, a medical club is said to have existed in Boston, which may still exist today, that had as its only constitutional requirement that electrocardiography was not to be mentioned in its meeting, not even a T wave. Fortunately for the freedom of man such a club can exist, but such attitudes muzzle freedom of scientific thought and discourse. The general ridicule and expressions of pessimism by the least informed were certainly heard widely. With the firm convictions and perseverance of the leaders and of those less well known, electrocardiography continued to develop until it has now reached a state at which even the greatest skeptics wish to know the electrocardiographic manifestations when they themselves develop coronary disease.

The proper recording of the electrocardiogram offers no difficulty, and an electrocardiograph is available to anyone; the interpretation of the tracing is the limiting factor and the greatest source of error. To interpret the records properly requires electrocardiographic knowledge and mature judgment, still a limitation of many clinicians. However, with ever increasing effort more and more physicians are learning to interpret the electrocardiogram. There is a need to continue to educate clinicians in this regard. A new shiny electrocardio

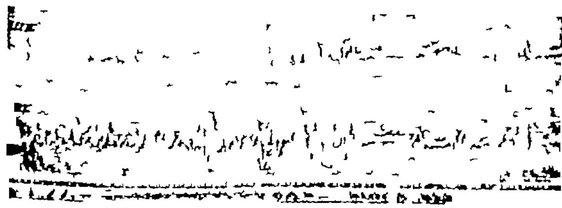


Fig. 17. The first recorded electrocardiogram of ventricular fibrillation in man without death. (Reprinted from Hoffman: Heart 3: 13, 191 .)

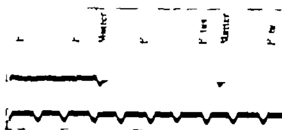


Fig. 18. First recording of the electrocardiogram of the mother and fetus. (Reprinted from Cremer: Munchen med Wchnschr 53:811, 1906.)

graph or fine recording do not constitute good electrocardiographs. Clinical electrocardiography can be no better than the man interpreting the tracing. Although known to many, this principle is too often forgotten and the patient suffers. It is not electrocardiography that is to be criticized but those who practice it. In the hands of the trained interpreter the electrocardiogram is a wonderful clinical tool; in the hands of the untrained, a dangerous weapon.

As with new drugs, so it is with new developments in electrocardiography; the most critical clinician succumbs to errors and difficulties which are detrimental both to the patient's health and his finances. Careful, methodical training in electrocardiography is needed and must be disseminated to all areas of the world to supplement the clinical study of the patient but never to replace it. As with Einthoven, Lewis, Wilson, and others of the past, the leaders in clinical electrocardiography today consider the electrocardiograph as merely a tool which should be properly integrated in the over-all study of the patient.

Einthoven was on a lecture tour in Boston when he learned that he had been awarded the Nobel prize in medicine. Before he had received official notification he was told of the newspaper announcement. He wondered whether this could be just an American joke or a misprint in the *Boston Globe*, but when he learned that the announcement was a Reuters news release he was then certain of the data and, of course, delighted.

To illustrate the modest and self-critical personality of Einthoven it is only necessary to cite two experiences that he had with the clinical applications of his galvanometer. Johann T. Peters, a practicing internist of Amsterdam, told me several years ago that he once had a wealthy Dutch patient who returned from Java to consult him about his heart. During the course of study, Dr. Peters suggested that he go to Leiden to have an electrocardiogram recorded with Einthoven's new electrocardiograph. Peters, then a young man and a great admirer of Einthoven, recognized the importance of the instrument. Peters advised his patient to be sure to give Einthoven 100 guilders for his services. The patient visited Einthoven's laboratory, indicated the purpose of his visit, and had a recording made which was later mailed to Peters. When the patient offered to pay, Einthoven replied that he could not accept the money because he did not see how the electrocardiogram could be of any real service to him. The patient insisted and Einthoven again refused, indicating that acceptance of the money would not be honest or just. How

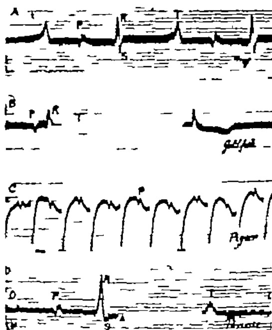


Fig. 19. Electrocardiograms from various animals recorded prior to 1913. T. Lewis by leading off from the limb with the heart unexposed. Electrocardiographic studies in animals were already beginning to have considerable influence upon the understanding of the human electrocardiogram. (Reprinted from T. Lewis: *Clinical Electrocardiography*, London, 1913, Shaw & Sons, Ltd.)

ever the patient loyal to Peters thanked Einthoven gathered his hat and coat and walked out leaving 100 guilders on a table as he left the laboratory

Samuel Levine of Boston tells of an interesting experience which occurred when Einthoven was lecturing in Boston at the time at which he learned of his Nobel award As Einthoven and Levine were standing in a hallway at the Peter Bent Brigham Hospital discussing a problem a technician emerged from the laboratory with a wet electrocardiogram in her hand approached Levine and interrupted the conversation saying Sorry to interrupt you Dr Levine but this electrocardiogram shows that your patient has a fresh infarct Should I notify the resident? Levine said Yes The technician left in a hurry and Einthoven astonished asked Dr Levine you mean the technician was able to recognize myocardial infarction from the electrocardiogram and without the assistance of a trained cardiologist? Levine assured him that this was correct

Little did Einthoven realize the extent and influence his electrocardiograph was then having on clinical medicine With the simplicity of use and interpretation of the tracing even lay technicians were already becoming expert One can only conjecture what his reactions would be today if he were to see the clinical applications of his instrument Many patients today insist on an electrocardiogram for a thorough cardiac evaluation Patients in the United States at least speak of T wave changes and inquire about such changes The cardiograph is a household word

Anyone who reviews the history of electrocardiography is impressed with the fact that Einthoven was a great man a simple humble person who was so modest and self-critical that he was astonished by the accomplishments of his instrument and work He was fortunate to observe personally the development of many fine things during his lifetime Little did he realize that that was only the beginning

In closing may I express my appreciation and thanks to all of you of Leiden and Holland for this opportunity to discuss briefly the developments in clinical electrocardiography since Einthoven s report in 1903 To participate in this event in recognition of Einthoven is one of the greatest honors and opportunities of my lifetime May medicine and science continue to flourish in Holland and the world for the health and happiness of mankind

REFERENCES

1 Waller A D Calculation of the inclination of the electrical axis of the heart J Physiol (London) 46 lx, 1913
2 Waller A D A demonstration on man of electromotive changes accompanying the heart s beat J Physiol (London) 8 229 1887
3 Waller A D Effect of respiration on the electrocardiogram and upon the electrical axis of the heart J Physiol (London) 46 h 1913
4 Waller A D Introductory address on the electromotive properties of the human heart Brit M J 2 751 1888
5 Waller A D On the electromotive changes connected with the beat of the mammalian heart and of the human heart in particular Phil T Roy Soc London 180 169 1889
6 Helmholtz H Geschwindigkeit einiger Vorgänge in Muskeln und Nerven Berichte über die zur Bekanntmachung geeigneten Verhandlungen der K Preuss Akademie der Wissenschaften zur Berlin 1854 p 328
7 Kolliker A and Muller H Nachweis der negativen Schwankung des Muskelstroms am naturlich sich contrahirenden Muskel Verhandl Phys Ges Wurtzburg 6 528 1856
8 Donders F C Rustende spierstroom en secundaire contractie uitgaande an het hart Onderzoekingen gedaan in het Physiologisch Laboratorium der Utrechtsche Hoogeschool 1 256 1872
9 Burdon Sanderson J and Page F J M On the time-relations of the excitatory process in the ventricle of the heart of the frog J Physiol (London) 2 385 1880
10 Einthoven W Die galvanometrische Registrierung des menschlichen Elektrokardiogramms zugleich eine Beurteilung der Anwendung des Capillar Elektrometers in der Physiologie Pflüger Arch ges Physiol 99 472 1903
11 Einthoven W Un nouveau galvanometre Arch Neerlandaises des Sciences Exactes et Naturelles 2 40 1901
12 Barron S L The development of the electrocardiograph in Great Britain Brit M J 1 720 1950
13 Cohn A E Recollections concerning early electrocardiography in the United States Bull Hist Med 29 469 1955
14 I memoriam Willem Einthoven Heart 14 v 1928
15 Einthoven W Weiteres über das Elektrokardiogramm Pflüger Arch ges Physiol 122 517 1908
16 Einthoven W Fahr G and de Waart A Über die Richtung und die manifeste Grosse der Potentialschwankungen im menschlichen Herzen und über den Einfluss der Herzlage auf die form des Elektrokardiogramms Pflüger Arch ges Physiol 150 275 1913

17. Einthoven, W., Fahr, G., and de Waart, A.: On the direction and manifest size of the variations of potential in the human heart and on the influence of the position of the heart on the form of the electrocardiogram, AM. HEART J. 40:163, 1950. (Reprint 1913, translated by Hebbel E. Hoff and Paul Sekelj.)
18. Einthoven, W.: The different forms of the human electrocardiogram and their signification, Lancet 1:853, 1912.
19. Flohil, A.: Vergelijkende roentgenphotographische en electrocardiographische onderzoekingen over de richting en de manifeste grootte van het resulterend potentiaal verschil in enige pathologische harten, Thesis, Leiden, 1918. (from summary translated by H. A. Snellen.)
20. Lewis, T.: Auricular fibrillation and its relation to clinical irregularity of the heart, Heart 1:306, 1910.
21. Lewis, T.: On the electrocardiographic curves yielded by ectopic beats arising in the walls of the auricles and ventricles, Brit. M. J. 1:750, 1910.
22. Lewis, T.: Electrocardiography and its importance in the clinical examination of heart affections, the analysis of cardiac irregularities, Brit. M. J. 2:65, 1912.
23. Lewis, T.: Interpretation of the initial phases of the electrocardiogram with special reference to the theory of limited potential differences. Seventh Mellon Lecture delivered before the Society for Biological Research, University of Pittsburgh School of Medicine, May 8, 1922.
24. Lewis, T.: Irregular action of the heart in mitral stenosis, the inception of ventricular rhythm, etc., Quart. J. Med. 2:356, 1909.
25. Lewis, T.: Lectures on the heart, New York, 1915, Paul B. Hoeber.
26. Lewis, T.: The pacemaker of the mammalian heart as ascertained by electrocardiographic curves, J. Physiol. (London) 41:53, 1910.
27. Lewis, T.: Mechanism and graphic registration of the heart beat, London, 1920, Shaw & Sons, 3rd edition, 1925.
28. Lewis, T.: Galvanometric curves yielded by cardiac beats generated in various areas of the auricular musculature. The pacemaker of the heart, Heart 2:23, 1910.
29. Lewis, T.: The mechanism of the heart beat, London, 1911, Shaw & Sons.
30. Lewis, T.: Clinical disorders of the heart beat, New York, 1912, Paul B. Hoeber.
31. Lewis, T.: Pain in muscular ischemia, its relation to anginal pain, Arch. Int. Med. 49:713, 1932.
32. Lewis, T.: Paroxysmal tachycardia, Heart 1:43, 1909.
33. Lewis, T.: Paroxysmal tachycardia, accompanied by the ventricular form of venous pulse, Heart 2:127, 1910.
34. Lewis, T.: Paroxysmal tachycardia, the result of ectopic impulse formation, Heart 1:262, 1910.
35. Lewis, T., and Cotton, T. F.: The P-R interval in human electrocardiograms and its relation to exercise, J. Physiol. (London) 46:lx, 1913.
36. Lewis, T., and Mack, E. G.: Complete heart block and auricular fibrillation, Quart. J. Med. 3:273, 1910.
37. Lewis, T., and Mathison, G. C.: Auriculoventricular heart block as a result of asphyxia, Heart 2:47, 1910.
38. Lewis, T., Meakins, J., and White, P. D.: The excitatory process in the dog's heart, the auricles, Phil. Tr. Roy. Soc. London 205:375, 1914.
39. Lewis, T., Oppenheimer, B. S., and Oppenheimer, A.: The site of origin of the mammalian heart beat; the pacemaker in the dog, Heart 2:147, 1910.
40. Lewis, T., and Rothschild, M. A.: The excitatory process in the dog's heart, the ventricles, Phil. Tr. Roy. Soc. London 206:181, 1915.
41. Durrer, D., and van der Tweel, L. H.: Spread of activation in the left ventricular wall of the dog, AM. HEART J. 46:683, 1953.
42. Durrer, D., van der Tweel, L. H., Berreklouw, S., and van der Wey, L. P.: Spread of activation in the left ventricular wall of the dog, two- and three-dimensional analysis, AM. HEART J. 50:860, 1955.
43. Hudson, R. E. B.: The human pacemaker and its pathology, Brit. Heart J. 22:153, 1960.
44. Herrick, J. B.: Clinical features of sudden obstruction of the coronary arteries, J.A.M.A. 59:2015, 1912.
45. Herrick, J. B.: Thrombosis of the coronary arteries, J.A.M.A. 72:387, 1919.
46. Smith, F. M.: Electrocardiographic changes following occlusion of the left coronary artery, Arch. Int. Med. 32:497, 1923.
47. Smith, F. M.: Further observations on the T wave of the electrocardiogram of the dog following the ligation of the coronary arteries, Arch. Int. Med. 25:673, 1920.
48. Smith, F. M.: The ligation of coronary arteries with electrocardiographic study, Arch. Int. Med. 22:8, 1918.
49. Pardee, H. E. B.: Clinical aspects of the electrocardiogram, New York, 1941, Paul B. Hoeber.
50. Pardee, H. E. B.: An electrocardiographic sign of coronary artery obstruction, Arch. Int. Med. 26:244, 1920.
51. Pardee, H. E. B.: Heart disease and abnormal electrocardiograms, with special reference to the coronary T wave, Am. J. M. Sc. 169:270, 1925.
52. Pardee, H. E. B.: The significance of an electrocardiogram with a large Q in Lead 3, Arch. Int. Med. 46:470, 1930.
53. Pardee, H. E. B., and Goldenberg, M.: Electrocardiographic features of myocardial infarction as affected by involvement of the septum and by complete and incomplete transmural involvement, AM. HEART J. 30:367, 1945.
54. Pardee, H. E. B., and Price, L.: Relation of myocardial disease to abnormalities of the ventricular complex of the electrocardiogram, AM. HEART J. 15:—, 1938.
55. Bousfield, G.: Angina pectoris, changes in electrocardiogram during paroxysm, Lancet 2:457, 1918.
56. Feil, H., and Siegel, M. L.: Electrocardiographic changes during attacks of angina pectoris, Am. J. M. Sc. 175:255, 1928.

57 Bayley R H On certain applications of modern electrocardiographic theory to the interpretation of electrocardiograms which indicate myocardial disease Am Heart J 26 769 1943
58 Bayley R H The electrocardiographic effects of injury t the endocardial surface of the left ventricle Am Heart J 31-677 1946
59 Bayley R H and LaDue J S Differentiation of the electrocardiographic changes produced in the dog by prolonged temporary occlusion of coronary artery from those produced by postoperativ pericarditis Am Heart J 28 233 1944
60 Bayley R H and LaDue J S Electrocardiographic changes of impending infarction and the ischemia injury pattern produced in the dog by total and subtotal occlusion of a coronary artery Am Heart J 28 54 1944
61 Bayley R H LaDue J S and York D J Electrocardiographic changes (local entricular ischemia and injury) produced in the dog by temporary occlusion of a coronary artery showing a new stage in the evolution of myocardial infarction Am Heart J 27 164 1944
62 Bayley R H LaDue J S and York D J Further observations on the ischemia injury pattern produced in the dog by temporary occlu ion of coronary artery incomplete diversion patterns theophylline T rever ion and theophylline conversion of the negative T patterns Am Heart J 2 657 1944
63 Boyd L J and Scherf D The electrocardiogram after mechanical injury of the inner surface of the heart Bull New York Med Coll 3 1 1940
64 Hill I G W Johnston F D and Wilson F N The form of the electrocardiogram in experimental myocardial infarction the later effects produced by ligation of the right coronary artery Am Heart J 16 309 1938
65 Johnston F D Hill I G W and Wilson F N The form of the electrocardiogram in experimental myocardial infarction Am Heart J 10 889 1935
66 Katz L N The significance of the T w in the electrogram and electrocardiogram Physiol Rev 8 447 1928
6 Lewman W G The history of electrocardiography Ann Med Hist 8 113 1936
68 Levy R L Barach A L and Bruenn H G Effects of induced oxygen want in patients with cardiac pain Am Heart J 1 187 1938
69 Macleod A G The electrogram of cardiac muscle an anal s which explains the regression or T deflection Am Heart J 1s 165 1938
0 Master A M and Oppenheimer E T A imple exercise tolerance test for circulatory efficiency with tandard tables for normal individual Am J M Sc 177 23 1929
71 Pruitt R Barnes A R and Essex H E Electrocardiographic changes sociated with lesions in the deeper layers of the myocardium experimental tudy Am J M Sc 210 100 1945
72 Rosenbaum F F Wilson F N and Johnston F D The precordial electrocardiogram in high lateral myocardial infarction Proc Central Soc Clin Res 18 35 1945
73 Rothschild M A Mann H and Oppenheimer B S Successive changes in the electrocardiogram following acute coronary artery occlu ion Proc Soc Exper Biol & Med 23 53 1926
74 Wilson F N The electrical currents associated with the heart beat Michigan Alumnus Quart Rev 4 12 1940
75 Wilson F N Barker P S Johnston F D Hill I G W and Cront G C The electrocardiogram in the earlier stages of experimental myocardial infarction J Clin Invest 12 993 1933
6 Wilson F N and Finch R The effect of drinking iced water upon the form of the T deflection of the electrocardiogram Heart 10 275 19 3
77 Wilson F N Hill I G W and Johnston F D The form of the electrocardiogram in experimental myocardial infarction septal infarcts and the origin of the preliminary deflections of the canine levocardiogram Am Heart J 9 596 1934
78 Wilson F N Hill I G W and Johnston F D The form of the electrocardiogram in experimental myocardial infarction the later effect produced by ligation of the anterior descending branch of the left coronary artery Am Heart J 10 903 1935
79 Wilson F N Johnston F D and Hill I G W The form of the electrocardiogram in experimental myocardial infarction additional observations on the later effects produced by ligation of th anterior descending branch of the left coronary artery Am Heart J 10 1025 1935
80 Wilson F N Johnston F D Hill I G W and Grout C C Form of the electrocardiogram in experimental myocardial infarction Proc Soc Exper Biol & Med 30 799 1933
81 Wolferth C C and Wood F C The electrocardiographic diagnosis of coronary occlu ion by the use of chest lead Am J M Sc 183 30 193 (Abstract Am Heart J 404 1932)
82 Wood F C and Wolferth C C Experimental coronary occlusion inadequacy of the three conventional lead for recording characteristic action current changes in certain sections of he m ocard um an electrocardiographic study Arch I t Med 51 771 1933
83 M ter A M Symposium on inhalational therapy notic effects on electrocardiogram produced by step test Bull New York Acad Med 26 401 1950
84 Wilson F N The distribution of the potential differences produced by the heart beat within the body and t its surface Am Heart J 5 599 1930
85 Wilson F N Johnston F D Macleod A G and Barker P S Electrocardiograms that represent the potential variation of a single electrode Am Heart J 9 447 1934
86 Wilson F N Johnston F D Rosenbaum F F Erlanger H Kossmann C E Hecht H Cotrim N Menezes de Oliveira R Scarsi

R and Barker P S The precordial electrocardiogram Am Heart J 2" 19 1944
8 Johnston F D and Lepeschkin E Selected papers of Dr Fra k N Wilson A Arbor 1955 J W Edward
88 Wilson F N Macleod A C and Barker P S Electrocardiographic leads which record potential rations pr luced by the heart beat at single point Proc Soc Exper Biol & Med 29 1010 193
89 Wilson F N Macleod A G Barker I S nd John ton F D The determination and the significance of the areas of the ventricular deflections of the electrocardiogram Am Heart J 10:46 1934
90 Wilson F N Macleod A G Johnston F D and Hill I G W Monoph sc electrical response produced by the contraction of injured heart muscle Proc Soc Exper Biol & Med 30 97 1933
91 Wilson F N Wishart S W and Herrmann G R Factors influencing distribution of potential differences produced by heart beat t urface of bod Proc. Soc Exper Biol & Med 23 6 19 6
92 Barnes A R Pardee H E B Whit I D Wilson F N Wolferth C C Bedford D I Cowan J Drury A N Hill I G W Parkinson J and Wood P H Standardization of precordial lead joint recommendation of the American Heart Association and the Cardiac Society of Great Britain nd Ireland Am Heart J 18 107 and 35 1938
93 Goldberger E A simple indifferent electrocardiographic electrode of zero potential and technique of obtaining augmented unipolar extremity leads Am Heart J 23 483 194
94 Goldberger E The aV₁ aV₂ and aV lead a simplification of tandard lead electrocardiography Am Heart J 24.3 8 1942
9 Joux A Senez J and Pierron J Diagnostic electrocardiographique Paris 1946 M son et Cie
96 Wilson F N Johnston F D Rosenbaum F F and Barker P S On Einthoven tri angle the theory of unipolar electrocardiographic lead and the interpretation of the precordial electrocardiogram Am Heart J 32.277 1946
97 Craib W H The electrocardiogram Medical Research Council London 1930 H M jesty Stationery Office
98 Craib W H A stud of the electrical field surrounding active heart muscle Heart 14 71 19
99 Macleod A G The electrogram of cardiac muscle the lengths of the tages of activity Am Heart J 15 40 1938
100 Macleod A G Wilson, F N and Barker P S The form of the electrocardiogram in trin.icord electrocardiographic deflections in animals and man Proc. Soc. Exper Biol & Med 2".586 1930
101 Wilson F N and Bayley R. H The electric field of an eccentric dipole in a homogeneous spherical conducting medium Circulation 1 84 1950
102 Wilson F N Bryant M and Johnston F D On the pos 1 il ty of con tructing an Einthoven triangle for a gi en subject Am Heart J 3" 493 1949
103 Wilson F N and Herrmann G R An experimental tudy of ncomplet bundle branch block and of the refractory period of the heart of the dog Heart 8 79 1921
104 Wilson F N and John ton F D The ector cardiogram Am Heart J 16 14 1938
105 Wilson F N Johnston F D and Barker I S The use of the cathode ray oscillograph the tudy of the monocardiogram J Clin Invest 16:664 1937
106 Wilson F N John ton F D and Kossmann C F The subst t tion of tetrahedron for the Einthoven triangle Am Heart J 33:594 1947
107 Wilson F N Macleod A G and Barker I S The accuracy of E thoven s equation Am Heart J 703 1931
108 Wilson F N Macleod A G and Barker P S The form of the electrocardiogram the character f the excitation w in auricular muscle Proc Soc Exper Biol & Med 2":558 1930
109 Wilson F N Macleod A G and Barker P S The form of the electrocardiogram opposed potential differences Proc Soc Exper Biol & Med 2":589 1930
110 Wilson F N Macleod A G and Barker P S The form of the electrocardiogram the mea electrical xi and the center of stimulation Proc Soc Exper Biol & Med 2".591 1930
111 Wilson F N Macleod A G and Barker P S The interpretation of the nitial deflections of the ventricular complex of the electrocardiogram Am Hear J 6:63 1931
112 Wilson F N Macleod A G and Barker P S The order of entricular excitation in human bundle branch block Am Heart J 305 1937
113 Wilson F N Macleod A G and Barker I S The potential variations produced by the heart beat the pices of Einthoven triangle Am Heart J .207 1931
114 Ashman R E timation of heart position from the QRS complex of the electrocardiogram Arch In t cardiol Mexico 16 139 1946
115 Ashman R Heart An Rev Physiol 6.319 1944
116 Ashman R Nociones fundamentales de electrocardiografia Rev argent cardiol 12 70 1945
117 Ashman R The normal human ventricular gradient the relationship between the magnitudes Aqrs and G and deviations of the RS-T segment Am Heart J 26 49 1943
118 Ashman R. An outline of electrocardiography New I ternat Clinics 1 193 1939
119 Ashman R A statistical tudy of the ventricular gradient and of the QRS complex of the electrocardiogram Arch Inst cardiol Mexico 1 .266 1945
120 Ashman R. Byer E and Bayley R. H The normal human entricular gradient factors which affect its d rection and ts relation to the mean QRS axis Am Heart J 25 16 1943

121 Ashman R and Byer E The normal human ventricular gradient factors which affect its manifest area and its relationship to the manifest area of the QRS complex Am Heart J 2 36 1943
122 Ashman R Ferguson F P Gremillion A I and Byer E Effect of cardiac cycle length upon magnitude of ventricular gradient Proc Soc Exper Biol & Med 59 47 1945
123 Ashman R Ferguson F P Gremillion A I and Byer E The normal human ventricular gradient the relationship between Aq and G and the potential variations of the body surface Am Heart J 29 697 1945
124 Ashman R Gardberg M and Byer E The normal human ventricular gradient the relation between the anatomic and electrical axes Am Heart J 26 4 3 1943
125 Yater W M Pathogenesis of bundle branch block Arch Int Med 62 1 1938
126 Burger H C and van Milaan J B Heart vector and lead Brit Heart J 8 15 1946
127 Becking A G T Burger H C and van Milaan J B A universal vectorcardiograph Brit Heart J 12 339 1950
128 Burger H C and van Milaan J B Heart vector and lead Brit Heart J 9 154 1947
129 Burger H C and van Milaan J B Heart vector and leads geometrical representation Brit Heart J 10 229 1948
130 Burger H C and van Milaan J B Measurement of the specific resistance of the human body to direct current Acta med scandinav 64 584 1943
131 Mann H Interpretation of bundle branch block by means of the monocardiogram Am Heart J 6 447 1931
132 Mann H A method of analyzing the electrocardiogram Arch Int Med 25 283 1920
133 Mann H The monocardiograph Am Heart J 15 681 1938
134 Mann H A new portable electrocardiograph Proc Soc Exper Biol & Med 23 19 1925
135 Schellong F Vektordiagraphie des Herzens als klinische Methode Klin Wchnschr 17 453 1938
136 Schellong F Heller S and Schwingel E Das Vektordiagramm eine Untersuchungsmethode des Herzens Ztschr Kreislaufforsch 29 497 1937
137 Schellong F and Schwingel E Das Vektordiagramm eine Untersuchungsmethode des Herzens uber die Bedeutung von Knotungen und Aufsplitterungen in QRS des Ekg Ztschr Kreislaufforsch 29 596 1937
138 Schellong F Schwingel E and Herrmann G Die praktisch klinische Methode der Vektordiagraphie und das normale Vektordiagramm Arch Kreislaufforsch 2 1 1937
139 Schellong F Ziele und Wege der Ekg Forschung Deutsche med Wchnschr 63 1337 1937
140 Hollmann H F and Hollmann W Das Einthovensche Dreieckschema als Grundlage neuer Elektrokardiographischer Fegt ter methoden Ztschr kl Med 134 732 1938
141 Hollmann W and Hollmann H E Neue elektrokardiographische Untersuchungen Ztschr Kreislaufforsch 29 465 546 193
142 Jouve A Buisson P Albouy A Velasque P and Bergier G La vectocardiographie en clinique Paris 1950 Masson et Cie
143 Sulzer R and Duchosal P W Die Grundform des menschlichen Vektorkardiogramms Schweiz med Wchnschr 71 59 1941
144 Sulzer R and Duchosal P W Principes de cardiovectographie la planographie Cardiologia 6 236 1942
145 Sulzer R and Duchosal P W Principes de cardiovectographie la stéréographie Cardiologia 9 107 1945
146 Wegner R Klinische Vektorkardiographie Darmstadt 1956 Steinkopff
147 Duchosal P W and Sulzer R La vectocardiographie New York 1949 S Karger
148 Schmitt O H and Simonson E Symposium on electrocardiography and vectorcardiography present status of vectorcardiography A M A Arch Int Med 96 574 1955
149 McFee R Comparison of heart vectors calculated with different systems of leads Circulation 2 128 1950
150 Frank E Theoretic analysis of the influence of heart-dipole eccentricity on limb leads Wilson central terminal voltage and the frontal plane vectorcardiogram Circulation Res 1 380 1953
151 Duchosal P W and Grosgurin J R The spatial vectorcardiogram obtained by use of a trihedron and its scalar comparisons Circulation 5 237 1952
152 Grishman A and Scherlis L Spatial vectorcardiography Philadelphia 1952 W B Saunders Company
153 Burch G E and Gerathewohl S J Some observations on heart rate and cardiodynamics during weightlessness Special Report U S Army Medical Services Research and Development Command Bioastronautics Research Unit Liaison to Army Ordnance Missile Command Presented at Second World-Fourth European Aviation and Space Medicine Congress Rome Italy October 27 31 1959 Aerospace Medicine 31 661 1960
154 Katz L N Electrocardiography Philadelphia 1946 Lea & Febiger
155 Lepeschkin E Modern electrocardiography Baltimore 1951 Williams & Wilkins Company
156 Katz L N The genesis of the electrocardiogram Physiol Rev 27 398 1947
157 Arrighi F P El eje electrico del corazon en el espacio con el estudio y empleo de las derivaciones sagitales Eje electrico y electrocardiograma en el plano sagital Prensa med argent 26 253 1939
158 Arrighi F P El eje electrico del corazon en el espacio en el plano frontal y en el plano sagital con el estudio y empleo de las derivaciones sagitales Tesis del doctorado año 1938 No 5051 impresa en 1938
159 Arrighi F P El eje electrico del corazon en el espacio en el plano frontal y en el plano sagital con el estudio y empleo de la derivaciones sagitales Buenos Aires 1938 El Ateneo
160 Wilson F N Macleod A G and Barker P S The distribution of the currents of actu

and of injury di played by heart muscle and other excitable tis ues U iver ty of Michigan Studies Scientific Series Vol X Ann Arbo 1933 Universit of Michigan Pres
161 Woodbury J W and Woodbury L A Membrane resting and act n potential from excitable tis ues Fed Proc 9 139 1950
162 Weidmann S Resting nd act on potentials of cardiac muscle Ann New York Acad Sc 6 663 1957
163 Cremer V M Über die direkte Ableitung der Aktionsströme des menschlichen Herzens vom Oesophagus und über da Elektrokardiogramm des Fötu München med Wchnschr 53:811 1906
164 Patten B M and Kramer T C The initia tion of contraction in the embry nic chick heart Am J Anat 53:349 1933

Developments in phonocardiography

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It has been felt that this symposium which aims at a survey of the present status of those fields in physiology and cardiology that were opened up by Einthoven should also include a brief account of phonocardiography. In fact, although Einthoven's contributions to phonocardiography are not so important as those to electrocardiography, they are still of outstanding value. His first and probably greatest achievement was to register the heart sounds by means of the capillary electrometer, thereby making analysis possible for the first time (Einthoven and Geluk, 1894). The carotid pulse and the apex beat were recorded simultaneously and served as reference tracings. It was pointed out that if one used a closed system for registration of heart sounds at the apex, only a cardiogram (apex beat tracing) would be obtained, and that a small air leak had to be added in order to abolish the predominant vibrations of low frequency and to free the way for the study of the heart sounds. It was further stated that the heart sounds were not sounds in the physical sense but complex vibrations, that is, murmurs. The systole was divided into two parts, the period of building up of tension and the ejection period. Although this idea was not original (Einthoven referred to earlier observations of a different, that is, hemodynamic nature by Hurthle and by Fredericq), and although the criterion for this division, namely, the time lag between the appearance of the first sound at the apex and of that at the aortic orifice, does not seem appropriate, yet this notion was a very important one. In the same publication the phonocardiogram of an experimentally produced aortic insufficiency was shown.

In 1906, when optico-mechanical methods for pulse recording, such as Otto Frank's, had already been introduced, Einthoven improved his registration technique by using the string galvanometer. At first one string galvanometer was available, by which either a single phonocardiogram ("cardiophonogram," as Einthoven used to call it), or the superposition of a phonocardiogram and an electrocardiogram in one tracing (Fahr[4]) could be recorded. Obviously, the value of such a superimposed electrocardiogram as a reference tracing was slight, and one wonders why Einthoven, who had been familiar for a long time with the registration of arterial and venous pulse curves, did not continue to use them as reference tracings. It must be inferred that he did not think this point of great importance, otherwise he would certainly have found ways of improving his pulse records. As it was, they did not show many details and were somewhat less satisfactory, as far as the venous curve is concerned, than were Gibson's of the same period. Both men (Gibson[5] and Einthoven) discovered independently and at the same time the third

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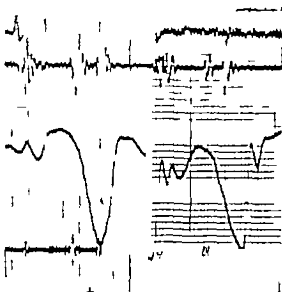


Fig 1 Constrictive pericarditis with third heart sounds Male born 1891 *Upper row* Electrocardiogram *Second row* Low frequency phonocardiogram (35 c.p.s.) *Third row* Venous curve *Fourth row* Intermediate frequency phonocardiogram (140 c.p.s.) *Left* Phonocardiogram taken at left sternal border third heart sound coincides with bottom of the diastolic depression in the venous curve (i.e. end of the rapid filling period of the right ventricle) *Right* Phonocardiogram taken at apex third heart sound occurs definitely earlier on the descending limb of the diastolic depression thereby indicating its left sided origin

heart sound is a normal although inconstant phenomenon—Gibson by means of auscultation Einthoven from his phonocardiogram But both of them were led astray in their interpretation by imperfect recording of the time relations between heart sounds and pulse curves Gibson attributed the third heart sound to closure of the atrioventricular valves supposing it to be simultaneous with the b wave (in accordance with Hirschfelder[7] now called h wave) in the jugular venous tracing Einthoven on the other hand could not find this b wave in his curves and thought that the third heart sound was due to after vibrations of the aortic valves

Battaerd[8,9] one of Einthoven's collaborators published records obtained with two string galvanometers showing simultaneously either two different phonocardiograms for instance taken at the apex and at the aortic orifice or a phonocardiogram and an electrocardiogram Photographic enlargement of these tracings and careful analysis of the vibrations revealed the presence of high frequencies up to 1,000 cycles per second The amplitude of these vibrations however was very small and now appears insufficient It was further shown that in the phonocardiogram taken at the apex initial vibrations of low frequency could be detected occurring only a few thousandths of a second after the onset of the QRS complex followed 0.06 second later by vibrations of higher frequency the first thought to be due to muscular contraction and the latter to valvular movement The value of the electrocardiogram as a reference tracing especially in irregularities of the heart was stressed and the differences as well as the similarities of auscultation and phonocardiography were discussed Rightly it was pointed out that whereas the ear shows a widely different response to varying frequency it is on the other hand capable of ignoring extraneous disturbances which the instrument faithfully records Battaerd's opinion (doubtless also that of his teacher Einthoven) was that phonocardiography should supplement not supplant auscultation

It has been stated already that Einthoven who laid the foundation stones for

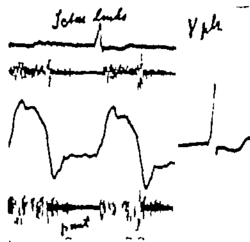


Fig 2 Mitral stenosis and insufficiency Female born 1909 *Left* Apex beat tracing taken with the patient lying on her left side and phonocardiogram Distinct delineation of first (rapid) filling phase in the diastolic part Phonocardiogram shows pansystolic murmur and short diastolic murmur starting after the opening snap The latter coincides with the bottom of the apex beat tracing (beginning of diastolic filling of the left ventricle) *Right* Precordial ECG taken at apex

both electrocardiography and phonocardiography was more successful in the development of the former than of the latter. Presumably this was due to the fact that phonocardiography is highly dependent on clinical and pathologic findings for its interpretation. It follows that the limitation of diagnostic facilities and knowledge of those years must have been a greater obstacle in the pathway of phonocardiography than of electrocardiography. Furthermore there was an unfortunate loosening of the psychologic ties between the clinic and the laboratory in spite of the well functioning physical connection between the two described in Einthoven's article on the telecardiogram. After the work resulting in Battaerd's thesis published in 1913 Einthoven did not add much to the field of phonocardiography except a technical improvement consisting in the construction of the string phonograph which he described with his pupil Hoogerwerf in 1924.[1] No further use of this instrument was made however during the few remaining years of Einthoven's life.

Time does not permit us to follow the further development of phonocardiography but we must look at how the subject stands today. The recording technique has been improved in many ways and the necessity of using filters (in the plural sense) has been established. Apart from spectral phonocardiography which interesting as it

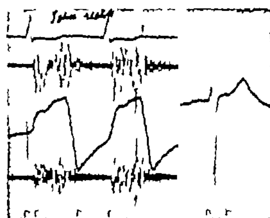


Fig 3 Same patient as in Fig 2 *Left* Apex beat tracing taken with the patient lying on her back. A clear distinction between rapid and slow filling phases. Opening snap precedes the point indicating beginning of diastolic filling (in this case of the right ventricle). *Right* Precordial ECG taken at apex.

is has yet to prove its clinical value, frequency bands of varying width and definition are being used. It would seem that efforts directed toward standardization such as were recently undertaken in this country by a committee of the Netherlands National Health Research Council T N O may be useful. It should be possible to establish an international agreement about the requirements for clinical phonocardiography which could yield comparable records from different hospitals. Obviously

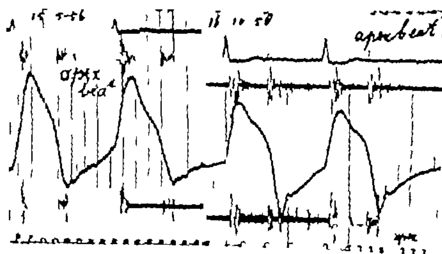


Fig 4 Mitral stenosis. Female born 1913. See text. *Left* Before operation. *Right* After commissurotomy.

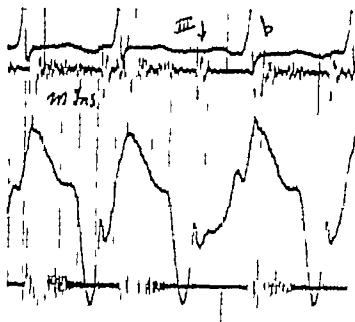


Fig. 5. Mitral insufficiency. Male born 1909. See text.

for research purposes there will always be the need of other than routine methods for example a study of the very high frequencies. At the present time however some cardiologists still have to be convinced that the aim of phonocardiography should not be to imitate auscultation nor to endanger it as a rival but to give supplementary information as was already clear to Einthoven.

Many *advances have been made in the* last thirty years but most of them were foreshadowed by subtle auscultatory observations especially from the French school of Potain, Vaquez and Laubry. (Parenthetically at the same time these clinicians acquired a large experience in recording cardiograms and pulse curves a field which unfortunately has lately been neglected even in Paris as appeared from a recent visit.) The six heart sounds (including the systolic ejection sound the opening snap of the atrioventricular valves and the four classic sounds) to which could be added the mid systolic click the summation gallop sound and the sound of *transient closure of the atrioventricular* valves have been identified and the origin of murmurs has been established to a large extent. Some of these although clinically important have been recognized as representative of functional that is relative nonorganic stenosis. To cite an example the relative pulmonic and tricuspid stenoses in atrial septal defect are responsible for the only (and diagnostic) auscultatory signs in this condition apart from the reduplicated second sound which is probably due to the concomitant bundle branch block. On the other hand all protosystolic murmurs belong to the same type and in fact as far as this murmur is concerned *phonocardiographic differentiation* between a slight or moderate pulmonary stenosis in atrial septal defect and a functional murmur due to increased cardiac output as in anemia may be very difficult if at all possible. So we are led back to the old concept of relative stenosis (and of course insufficiency) of valves.

However in our opinion the chief gain is that lately we have learned to look at the phonocardiogram from a hemodynamic point of view and it has become clear that the phonocardiogram may be used as a reliable guide in hemodynamic interpretation. This is only true on one condition however. One should not be satisfied with the *electrocardiogram* as a *reference* tracing for timing the phonocardiographic events; all available information should be used. This means that simultaneous recording of various pulsations such as those of the jugular vein the carotid subclavian

and femoral arteries of the heart itself at the apex and elsewhere in the precordial region is indispensable. If necessary, further information can be obtained from simultaneous pressure tracings obtained by heart catheterization and (or) electrokymograms of the heart and the great vessels.

Another old but clinically very important notion has come back to us by way of modern phonocardiography. Obvious as it may be, its implications have not been generally recognized as yet. We are referring to the independence (limited, of course, but hemodynamically important) of the right and left heart. Consequently, a certain extent of asynchronism is possible and does occur even under normal circumstances. In pathologic conditions the asynchronism may be greatly increased and the normal sequence may be reversed. Splitting of the second

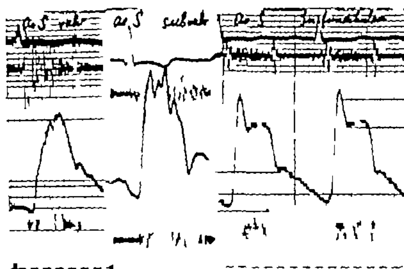


Fig. 6. Aortic stenosis. *Left*, Valvular type. Female, born 1909. Phonocardiogram shows ejection sound, diamond-shaped systolic murmur and late aortic part of the second sound (reversed splitting). Carotid pulse. See text. *Center*, Subvalvular type. Male, born 194[illegible]. See text. Diamond-shaped systolic murmur is followed by protodiastolic murmur. *Right*, Infundibular type. Female, born 1907. See text.

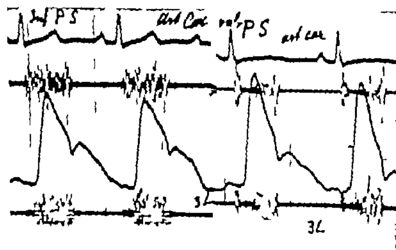


Fig. 7. Pulmonic stenosis. See text. *Left*, Infundibular type. Female, born 1946. *Right*, Valvular type. Male, born 1942.

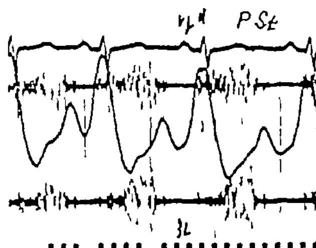


Fig. 4. Valvular pulmonic stenosis. Female born 1936. Venous curve with phonocardiogram. See text.

sound was already explained by Potain on the basis of nonsimultaneous closure of the aortic and pulmonary valves. In the same way we have now come to accept the existence of separate third and fourth sounds from both sides of the heart, although actual reduplication is rare. Sometimes, however, a third sound from both sides of the heart may be found (Fig. 1), and it is highly probable that the so-called fifth sound is no other than a right-sided third sound. Furthermore, the occurrence of a right-sided opening snap was demonstrated by Leatham in cases of atrial septal defect.

It should be mentioned here that the apex beat, which is a very rich source of information in clinical practice, especially in relation to the diastolic filling of the heart and the impact of atrial contraction, may also constitute a problem by having a left-sided or right-sided (or sometimes a two-sided) origin. The finding of a right-sided apex beat is in itself an important clinical sign, for example, as an indication of the true nature of a systolic apical murmur in the case of a severe mitral stenosis without distinct diastolic rumble but with pulmonary hypertension and relative tricuspid insufficiency. The same finding may also aid in differentiating atrial septal defect of the ventral and dorsal (so-called primum and secundum) types.

How does one recognize the right-sided apex beat? Partly by its rounded diastolic contour and by comparison with the jugular venous tracing, but better still by the aspect of the electrocardiogram taken exactly at the place of the apex beat, provided that this electrocardiogram shows a typical pattern (qR or qRs for the left and rS for the right side), which is unfortunately not always the case (Figs. 2 and 3). Our experience so far, both in connection with the phonocardiographic tracings and with the epicardial leads obtained during operation, seems to indicate that this is a reliable sign.

In closing, we wish to make it clear that the usefulness of the pulsation tracings is not limited to the interpretation of the phonocardiogram, but that their pattern in itself gives extremely valuable indications pertaining both to the diagnosis and to the severity of heart disease. In fact, the degree of mitral stenosis, pulmonary stenosis, and aortic stenosis, to mention a few operable conditions, can be fairly well assessed from the phonocardiogram in conjunction with the pulsation curves—so much so that the need for right-sided or left-sided heart catheterization is thereby greatly reduced for practical purposes. The same applies to the localization of aortic or pulmonary stenosis (valvular or infundibular with the subvalvular region between them). Valuable information in this respect may be obtained, of course, with selective angiocardiography, but as long as this cannot always be expected to

be quite innocuous especially in the left heart the harmless and simple procedure of taking a phonocardiogram with pulsation curves which in most cases is sufficient to localize and to estimate the stenosis should be the first and often even the final approach

A few examples may serve to illustrate these statements

The first (Fig 4) concerns the pattern of the apex beat tracing in particular of the initial rapid phase of diastolic filling in mitral stenosis before and after operation in the same patient In both cases the opening snap is clearly visible and is seen to coincide with the beginning of diastolic filling Before operation however the rapid initial phase is very small it is virtually normal after commissurotomy The next tracing (Fig 5) shows a further exaggeration of the rapid filling phase and the occurrence of a sharp peak at the end of it in mitral insufficiency There is no opening snap but a third heart sound is present which coincides with the peak

Next Fig 6 shows the carotid pulse contour and the phonocardiogram in the three different localizations of aortic stenosis In all three the ejection time is lengthened and the aortic part of the second sound is late when it is visible In the valvular type the ascent of the carotid pulse is slow and leads to a plateau with coarse vibrations there is also an ejection sound except in some cases which show extensive calcification of the valves The infundibular type in which case the stenosis is well below the valves in the muscular part of the ventricle shows a steep rise of the carotid pulse followed by an early descent to a horizontal plateau without vibrations There is no ejection sound Finally the immediately subvalvular variety shows a carotid pulse contour very similar to the valvular type although the ascending part is steeper So far no ejection sound has been found in these cases in our material

The last example concerns valvular and infundibular pulmonary stenosis The difference in the systolic murmur is obvious (Fig) an almost equal amplitude throughout the whole of systole in the infundibular type with a frankly crescendo murmur in the valvular type of marked or severe stenosis Both murmurs exceed the point of the carotid incisure indicating lengthening of right sided ejection time The venous curve in a case of severe pulmonary stenosis (Fig 8) shows exaggerated A waves and the phonocardiogram a fourth sound with a slight presystolic murmur all due to increased right atrial pressure

It is possible to give other examples but we hope that those which have been presented will suffice to explain the present growing interest in phonocardiography

REFERENCES

1 Einthoven W and Geluk M A J Die Registrierung der Herztone Pflüger Arch ges Physiol 57 617 1894
2 Einthoven W Flohil A and Battaerd P J Th A Het registreren an de menschelijke harttonen met de snaargalvanometer Nederl tijdschr geneesk 40 818 1906
3 Einthoven W Flohil A and Battaerd P J Th A Die Registrierung der menschlichen Herztöne Pflüger Arch ges Physiol 11 461 1907
4 Fahr G On simultaneous record of the heart sounds and the electrocardiogram Heart 4 147 1913
5 Gibson A G The significance of hitherto undescribed w in the jugular pulse Lancet 1907 p 1380
6 Einthoven W Wieringa J H and Snyders F P Ein dritter Herzton Pflüger Arch ges Physiol 120 31 1907
7 Hirschfelder A D Some ariations in the form of the enous pulse Bull Johns Hopkins Hosp Nos 195/196 265 1907
8 Battaerd P J Th A Verdere grafische onderzoekingen over de acustische erschijnselen an het hart in normale en pathologische omstandigheden Thesis Leiden 1913
9 Battaerd P J Th A Further graphic r searchs on the acoustic phenomena of the heart in normal and pathological conditions Heart 6 No 2 1915
10 Einthoven W and Hoogerwerf S Der Saiten phonograph Pflüger Arch ges Physiol 204 275 1924

A day's discussion on electrocardiography

Summary of final remarks by Dr G Giraud

Dr Giraud having been asked to speak and at the same time to summarize the papers given during the afternoon and to direct the discussion began by offering his thanks to the School of Medicine in Leiden and to Professor Snellen for the honor which they had bestowed upon him

The afternoon had been devoted to three papers all of unusual interest but differing much in nature The first had been given by Dr H C Burger the second by Dr G E Burch and the third by Dr H A Snellen

Dr Burger's paper In his paper on heart vector and leads Dr Burger expounded his personal views with renewed vigor He criticized the present method of vectorgraphic delineation of the heart's activity and condemned the old methods which are geometrical and intuitive He has criticized the fallacious argument based on the equilateral triangle and also that related to the regular tetrahedron of Wilson He has given us a rational foundation of electrocardiography and of vectorcardiography regarded as functions of linear equations Furthermore he attacks the systems developed by Frank Schmitt and McFee which are based on the hypothesis of a homogeneous material and in contrast has expounded his own theories based on consideration of a material with heterogeneous characteristics

At the present time Schmitt finds it necessary to use fourteen electrodes whereas McFee employs nine and Burger keeps five but Burger has suggested that if there is still some possibility of standardization the chances thereof are not great and perhaps they are not practicable

The speaker remarked that all those present must have been aware of the warmth with which Dr Burger developed his argument but since Professor Rijlant of Brussels was present it was highly desirable that he should be asked to give his views Nothing could be more profitable than debate between these two eminent physiologists because each is a master in the field of modern methods of vector cardiography In consequence Professor Rijlant was then asked to speak

Discussion by Prof Dr P Rijlant Burger's attempt to establish a statistical correlation between vectorcardiographic methods as they are used today emphasizes the over all usefulness of the vectorcardiographic approach They also call our attention to the important discrepancies

These methods are adequate for diagnosis and perhaps also for clinical research They are quite simple and do not call for extensive or intricate equipment

On the other hand research in physiologic or medical laboratories has a need for more accurate and less empirical methods These methods should be adequate not only for human vectorcardiography but also for experimental research on the exposed or isolated heart of laboratory animals

The easiest and safest approach is the integration of all the information available at the surface of the body or of the exposed heart to build up a dipole equivalent of

*Translated by Geoffrey C P [illegible] M D M R.C.P Hitchin Hertfordshire England

the electrical generators inside the heart

The whole of the body surface is explored by seventy two regularly spaced electrodes either in man or the intact animal For the isolated or exposed heart twenty regularly spaced electrodes enclose the heart in a regular dodecahedron

To provide for a precise location of the electrodes and also to speed up the procedure the electrodes are permanently affixed on an elastic jacket or on an elastic network In man or intact animal the skin is rubbed with a conducting paste

The electrodes feed current into a three dimensional conducting homogeneous medium of non Euclidean geometry This conducting medium is built up by several thousands of identical resistors it is symmetrical in respect to three orthogonal planes Distribution of current inside the network at a safe distance from the input electrodes is such that direct measurement of the orthogonal axes of the dipole moments can be attempted Control experiments on models have shown that the accuracy is better than 95 per cent

Simultaneous recording of the three dipole moments provides for the vertical transverse and anteroposterior vectorelectrocardiograms as opposed to the commonly used scalar electrocardiogram and the frontal sagittal and horizontal vector cardiograms

A precise analysis of either the QRS the T or also the S T components is made possible by the use of resolvers that provide for the rotation in space of the electrical axes This rotation has shown that in at least 95 per cent of several thousand normal young individuals the QRS loop lies in a simple plane The T wave is not located in the same plane There is no rotation of the T vector in normal man dog or rabbit The so called T loop is due to interference with the S T component This S T component is present in at least 30 per cent of normal individuals its size is about 15 to 40 per cent of the size of the T component It is always oriented at right angles to T which makes for the T loop The end of the S T component is always four hundredths of a second before the end of the T wave

Although the clinician does not feel for the time being the need of more accurate vectorcardiographic methods experimental research is dependent on a more precise knowledge and on methods that provide for adequate means of measurement of either physiologic or pathologic variations of the global electrogenesis of the heart

To increase the accuracy of the methods *employed* recording on magnetic tape is used as a method for storing the information and these records can be analyzed at leisure at a later stage This storing of information should be considered in the near future as a routine method to shorten the time needed to collect the available information the extensive analysis being postponed till a more suitable moment Perhaps this will provide for a sharing of the burden by the clinician who collects the information and the physicist who analyzes the information

Dr Burch's paper In his paper Dr Burch gave a most dramatic picture of the clinical developments in electrocardiography since the time of Einthoven Dr Giraud suggested that it was highly desirable that all present should have the text of this exposition which had up to that time never been made with such clarity and completeness

Dr Giraud also thanked and congratulated D Burch for his remarks and pointed out that he had not gone further than the introduction of external precordial methods in using the leads He expressed the hope that a new chapter had been opened which may be added to those already described in such a masterly manner He had in mind electrocardiography with leads taken from the cavities of the heart and also the use of similar methods with leads taken directly from the outer surface of the heart in man this procedure now being possible because of the advances made in thoracic surgery Epicardial readings as used in animal experiments have provided most valuable information This method of investigation has made it possible to study the behavior of certain parts of the auricles which previously had been out of reach In this connection the experiments carried out by Paul Puech were of interest

Endocardial electrocardiography as introduced into France by Lenegre and elaborated by the school of Montpellier

has to its credit much new evidence The procedure has been known for some years and is in present use it has thrown much light on certain areas about which we knew little before A true endocardial and direct method has been made possible in the right heart and sometimes in the left heart in the presence of septal defects Alternatively the behavior in the latter has been examined by retrograde methods through the arterial system It has been possible to investigate all parts of the various heart cavities and to record either the sum total of the electrical changes occurring in the heart as a whole or those which occur at the point at which the electrode is resting and at which the greatest electronegative deflection is most marked Dr Giraud remarked that this was not the occasion for describing all the new information gained by this new procedure but he could point out that during fibrillation of the auricle there were many foci of activity in sundry parts of that cavity which exhibited variations in frequency Furthermore these methods had thrown new light on the Wolff Parkinson White syndrome We now know more about the electrical changes originating in the coronary sinus of the changes occurring in Tawara's node and of those in the main part of the bundle of His Further information has also been obtained of the myoneural roots in the neighborhood of the coronary sinus which are found before regrouping in Tawara's node The waves of activity in these various parts have now been elucidated with great exactness this being a new development in 1960 Further studies are being carried out in stages not a term passes which does not give us new information All this has been possible because of the magnificent work of Einthoven

Dr Snellen's paper The third paper was that read by Professor Snellen who dealt with phonocardiography It was at this moment of Dr Giraud's address that Dr Snellen interrupted to point out that the time allotted for the papers in the afternoon had passed and that the moment had come to receive the family of Willem Einthoven this being the real purpose of the commemorative meeting

However the speaker asked Professor Snellen's permission to make a few remarks on the very fine paper which Dr Snellen had submitted

Dr Giraud pointed out that in the field of phonocardiography the Professor was like an apostle who could read in the tracings all sorts of things which others had failed to observe This could only be possible by a most perfect technique and in the light of much experience and great powers of observation One has to admit that Dr Snellen can find evidence from his tracings of a most exact and subtle nature which no other person has yet found possible

He has demonstrated the parallelism which may be shown between direct intracardiac catheterization and the information obtained by graphic methods He has defended the information obtained mechanically which tends today to be so easily forgotten but which in the time of Marey was so widely and so informatively used

Dr Snellen has even been able to describe certain indications in important cases whereby he can dispense with the information given by catheterization in considering certain operative procedures Speaking for himself he felt that in many of his opinions he was right although it was well known that a decision to operate could rarely be justified on one point of evidence alone All possible information and all information gained by metrical methods should be summarized and related to the clinical findings One could not be too well informed and in this respect the path shown by Professor Snellen has led to a rich harvest both now and for the future He would nevertheless point out that the cardiologist and also the general physician found it necessary to synthesize all the information about the patient which could be obtained

At this point some members of Einthoven's family including his two daughters and his grandson entered the meeting together with the official representatives of Leiden University to hear the reading of the two commemoration papers of Einthoven's former assistants de Waart and Regnier

Einthoven Commemoration

A. de Waart, M.D.

The Hague, Netherlands

During the years I worked with Einthoven, i.e. 1909-1913, Leiden was a very quiet little town. There were hardly any automobiles; at any rate none of the professors had an automobile. A horse tram connected the station with the Hogewoerd, passing the Breestraat with moderate speed. Along the Rijnsburgerweg, then a narrow road allowing a beautiful view over the meadows as far as the old castle of Poelgeest, there was a primitive steam tram. I lived in that Rijnsburgerweg just across the toll which at that time separated Leiden from Oegstgeest. This was the favorite road Einthoven chose in the evenings for his stroll. Since the time of his student days at Utrecht he had liked very much to walk and to ride on bicycle. Going to his laboratory he always crossed Leiden on bicycle and in case of rain was protected by a very special coat, the kind which was also worn by the celebrated pianist Pembauer. On the last Saturday of each month Einthoven could be seen at the station wearing a top hat on his way to the monthly meetings of the Academy of Sciences. He lived at that time in the Oegstgeesterlaan, now called Boerhaavelaan. Occasionally we walked together and sometimes we discussed the textbook of electrocardiography which he was writing and the difficulties arising from the fact that new discoveries continuously loomed up which he liked to include in this work. I think this book never appeared as such, but later on became the basis for his posthumous monograph "Die Aktionsströme des Herzens" in Bethe's Handbuch, 1928, which remains a masterpiece and still ought to be read by anyone who concerns himself with this branch of science.

I was asked to discuss Einthoven's personality *without* laying too much stress on his work. This is rather difficult. Work and personality cannot be separated entirely, because the personality leaves its impress on the work and shows itself in the work.

Moreover, to discuss his personality by itself is not at all in Einthoven's line. He did not attach much value or importance to his own personality. What he valued was objective and honest science, and what he admired was Nature.

What we call character seems partly hereditary and partly acquired. The upbuilding of character occurs *partly* at home, but also in a good school and in a good university, under the influence of good masters. Einthoven's scientific mind developed under the influence of Donders. He often spoke to us of Donders, but also of other classic figures such as Helmholtz, du Bois Reymond, Johannes Müller, and I am convinced that the lives of those men inspired him and helped him to develop his own personality.

In Einthoven's work we notice again and again how he persevered. He could point out to a new assistant on his very first workday the necessity of persevering

Address given June 23, 1960, at Leiden University by Dr. A. de Waart, Professor Emeritus of Physiology, in commemoration of the centenary of the birth of Willem Einthoven (1860-1927).

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He used to say: "Perhaps you read books about scientists making a new discovery each day. These books don't tell the truth. Often you have to spend several months only on the improvement of an arc lamp or another number of months only on locating a leakage in a vacuum pump."

As a true investigator, Einthoven thought as much of what we are ignorant of as he did of what already had been made clear. His chief interest was always in the territory which had not yet been traversed. He was a real explorer and pioneer. He sought the facts of life in adventures beyond the frontiers. He addressed Nature herself and penetrated to the center of her mysteries. His ingenious and inventive imagination served to indicate where and what the problems were, and to suggest and find methods for solving them. And his perseverance brought him to the solution. In this he resembled in many respects Helmholtz, who describes the invention of the ophthalmoscope as follows: "It was first so difficult that I doubt if I should have persevered unless I had felt that I must succeed."

Again and again Einthoven showed this perseverance in work and thought. Experimenting with the capillary electrometer, he studied this instrument for not less than 7 years (1893-1900), meanwhile also persevering in inventing and constructing his *string galvanometer, which he described in* 1901, publishing the first human electrocardiogram recorded by it in 1902. In 1903 he states: "Ich habe schliesslich ein Instrument herstellen lassen, das ... im Stande ist das menschliche Elektrokardiogramm unmittelbar in nahezu richtigen Verhaltnissen zu schreiben." This simple word "schliesslich" reflects perseverance, working hard daily for many years. And still he was not satisfied. His most perfect instrument came in 1926, and, working in cooperation with his son, he developed in 1923 the vacuum galvanometer, which was also used in the wireless of those days. But this latter instrument he had already planned in his papers 19 years before, in 1904, so that here again we see his perseverance.

We meet this mental trait again in the development of the triangle scheme. As early as 1896 and 1900 (capillary electrometer work with de Lint) and in 1908 (string galvanometer work with Vaandrager) he discussed the possibility of determining from the electrocardiogram "die Lage des Herzens oder der Herzachse," and persevering, he announced the triangle scheme in his Chelsea lecture of 1912.

More examples of his great perseverance would be easy to find. Suffice it to say that he was not content when there was still reason for doubt; he did not rest before he hit the mark.

Einthoven's sole motivation in his work was to discover the truth in many fields of physiology. Moreover, he lived to see his services to science applied with great success in the clinics. He promoted this success himself by recording (tele)cardiograms and phonograms of patients; for many years his laboratory afforded the sole place in the world where this could be done. He was always ready to assist his clinical colleagues and general practitioners and their patients, even if he had to interrupt other activities.

I told you already that Einthoven did not attach special value to his own personality. *Modesty was one of his principal* traits. He remained as much as possible in the background. Even when he talked about his own work, he tried to conceal his own name. In his rectorial address of 1906, neither his name nor that of his laboratory can be found in the discussion of his fundamental researches on the electrocardiogram, the electroretinogram, the vagus currents, and the heart sounds. He never allowed anything about himself to enter the newspapers. All jubilees were kept out of the press and he was absent from Leiden on such occasions.

In 1925 it was made possible for me to visit a number of universities in the United States. Quite by chance I passed through many institutes and laboratories where Einthoven had been some months before. Everywhere it proved that he had created a feeling of friendship and intimacy by his broad-minded and genial personality. He had been involved in many scientific discussions but in his usual way he always kept his own person in the background. For example, in Cleveland, differing with Wiggers concerning the identity of electrical and mechanical activities of heart

muscle he pointed out that investigators should perhaps expend more energy in attempts to harmonize differences rather than to gather more and more experimental evidence in favor of a previous conclusion and he said finally The truth is all that matters what you or I may think is inconsequential

During his stay in America he was awarded the Nobel prize Interviewed by journalists about his work he said I cannot expose to you my own work other people may do that if they like

Having seen in Boston the work of Forbes who combined the string galvanometer with radioamplification in nerve research I asked in the autumn of 1925 Einthoven's opinion about these experiments His answer was This has also been done by others but they got disappointed Afterward I discovered that he himself had done it but he never told me this personally

Einthoven lived at that time in a kind of reconstructed farm on the banks of the Old Rhine There he had a comfortable and quiet round study which was a part of an old mill surrounded on all sides by a balcony permitting a nice view in all directions

Besides his will to persevere and his modesty we want to stress his honesty and idealism

He always gave others the credit and honor they deserved

In 1891 commemorating the late Isebree Moens he states that the Leiden professorship was for the first time offered to that scientist rather than to himself In 1885 in his paper on the vagus effects on bronchial musculature he praises MacGillavry for his former researches on this subject In 1895 describing his new method for correcting the tracings of the capillary electrometer he calls the older method of Burch eine vorzugliche Arbeit In 1906 he states that the idea of connecting his laboratory to the hospital for the purpose of taking telecardiograms originated with Bosscha In 1907 giving the first records of the third heart sound he does not omit to praise the skill of Dr Gibson of Oxford who was the first to hear this sound In 1916 after proving that Gaskell's opinion about the electrical vagus effect on the heart was not valid he remarks nevertheless Wir mochten an dieser Stelle betonen dass wir obgleich Gaskell's Schlussfolgerungen bestreitend seine Arbeit doch gern anerkennen Es sei daran erinnert dass sie ausgefuhrt wurde in einer Zeit wo die elektrotechnischen Hilfsmittel weniger vollkommen waren als heutzutage Seine genaue Untersuchungen uber den Bau und die Innervation des Schildkroten herzens verdienen unsere Bewunderung und es ist ihm zu verdanken dass die vorzuglichen Eigenschaften dieses Organs die es besonders zum Gegenstand physiologischer Untersuchungen eignen allgemein bekannt geworden sind

And how often did Einthoven not value highly the work of Sir Thomas Lewis? Even when receiving the Nobel prize in Stockholm in 1925 he said in regard to Lewis Without his valuable contributions I doubt that I should have had the honor of appearing before you today

Einthoven certainly also was an idealist

Idealism has been a very pronounced attribute of great masters of medicine It expresses itself in a strong desire to pursue ideal ends at the cost of the ordinary prizes of life wealth material power and physical comfort But not always have the motives of scientists been purely altruistic Examples could be given of a master who patented an antitoxin avowedly with the intention of gaining money for further research but at the same time raising the cost of this antitoxin to the patients or of another master who secured for himself a patent for his method of narcosis But Helmholtz gave his ophthalmoscope freely to medicine and Pasteur gave his great discoveries freely to the world Einthoven never aimed at earning money by his work He already fully described his string galvanometer in 1901 He gave it freely to medical and physical science in his paper of 1909 Die Konstruktion des Saitengalvanometers He freely helped trustworthy concerns to duplicate it He gave every possible information to Williams who built the first instrument in America and promoted development of electrocardiography in that country He kept away only those people who intent on the making of money produced imperfect instruments and thereby caused much

misunderstanding in science. Honest and scientific people always had free access to the laboratory.

Concentration on research requires peace of mind. If an investigator is married and has a family, their happiness and contentment are important to him. Einthoven himself has often testified that he had a happy family life, and we were all aware of it. Mrs. Einthoven greatly aided her husband to proceed in his academic work. Out of that happy and sound family atmosphere also emerged the son Willem Frederik, who played a fundamental role in the birth of the vacuum galvanometer, and who later on gave to Java a brilliant institute of radiotelegraphy. We often met this son in the laboratory when he was just a young boy. He showed a remarkable interest and ability in mathematical, mechanical, and electrical problems, and followed in his father's footsteps, sometimes even preceding him. (He died as a prisoner of war in Tokyo in 1945.)

The original work performed in the institute of physiology attracted many distinguished visitors, e.g., Madame Curie, Pavlov, Samojloff, Waller, Westerlund, Jolly, Mislawski, Lewis. Sincere international contact and friendship existed.

Einthoven kept his laboratory active and pliable by never trying to build a permanent staff. Junior men and foreigners were encouraged by being given attractive work. As a rule they had consecutive periods for research and for teaching in the practical exercises. The didactic lectures were given by Einthoven himself. But here also he proved his modesty. If a man of teaching experience asked to attend these lectures, Einthoven said, "Don't waste your time, it is not worth while. I make too many mistakes." The strain of intense mental effort never affected his kind attitude toward medical students. He could understand that students cannot absorb in two years all the knowledge that professors gain in a lifetime. He was very humane in his examinations, but always honest and not weak. In our historical museum a letter can still be found in which he reprimands in rather strong terms a man who did not live up to his expectations.

Scientific work with Einthoven was not at all one-sided. Since most of the experiments could not be carried out without an assistant, the members of the small staff worked as a rule in pairs, each acting as assistant to the other on alternate days. Consequently they learned in many ways under Einthoven's guidance, and it was possible for nearly all not only to get practical experience in experimental and clinical electrocardiography and phonography, but also in electrophysiology of different nerves and muscles, and even in the x-ray technique of those days. We all developed our own photograms, taken on glass plates, and spent part of our life in the dark room. Handling the original and for some time the sole galvanometer with its at that time unsurpassed merits was not so difficult. Inserting a new string, however, was more complicated and was performed only in the presence of the professor. Yet the same string might last many years and be used in the most divergent investigations.

A century has passed now since Einthoven's birth. This centenary is not a cause for grief. It is a cause for rejoicing and thankfulness, remembering his great personality and contributions to science, to his university, and to international friendship.

The instruments with which and the surroundings in which we work today have changed immeasurably from what they were before; additional experiments will always be necessary to fill the gaps in our knowledge, but if we are to succeed, the spirit in which we work must remain the same as that in Einthoven's days. As in those days, we must realize that science is and has to be an international tree bearing fruits for the well-being of mankind, uniting peoples and nations all over the world.

After Dr. de Waart's paper a short record adapted from a dictation by Einthoven on an Edison phonograph was heard. Its subject was the telecardiogram, i.e., the electrocardiogram made in Einthoven's laboratory of a patient who was in the University hospital at a distance of a mile. This text was ultimately published in Bethe's *Handbuch der Physiologie*.

In memory of Einthoven*

*M. Regnier, M.D.***
Brussels, Belgium

I must ask you to excuse the emotion which I feel in finding myself among you to commemorate the centenary of the birth of Willem Einthoven, and also for the deep feeling which moves me when I think of the honor that you have given me in asking me to speak. I will endeavor, as a representative of Einthoven's former foreign assistants, to express in modest terms our feeling for his splendid personality and for a man who was beloved because of his apparent severity, a man who was such a complete individual by reason of the exquisite balance of his outstanding scientific, human, and moral qualities.

Professor De Waart has drawn attention in a masterly manner to the greatness of Einthoven's character, the constancy of his life, and his ideals. He has described his modesty of spirit, his scrupulous respect for the work of others, his unselfishness of thought, charity of heart, and the general aim of his life. Without thinking of himself, Einthoven aimed at knowing and discovering truth in Nature through all living beings so that all men might benefit from an increase in knowledge. To this end he promoted rigorous scientific enquiry in many fields, but particularly in the field of physiology and also in the field of disease, in which there is a general deviation from the physiologic state.

I will endeavor to describe in a few words the development of the work of the Master, who made such an outstanding contribution to recording the curves which illustrate in a real and exact manner the electromotor phenomena observed during the contraction of the heart. In studying this evidence and in developing new techniques, he made intelligible the functions of the healthy and of the diseased heart. A development of this kind could only originate with a man who was not only well based in the sciences but also had the necessary human qualities which permitted him to make use of his knowledge in clinical science and thereby to give aid to his fellow man. The pure physiologist and with him the philosopher were able at one bound to traverse the space separating the pure from the clinical sciences.

Before turning to the work of Einthoven in the field in which he was the great pioneer, I will refer briefly to the work of Matteucci in 1843, and that carried out by Koelleker and Muller in 1856. They were able to show that the contractions of the heart in the pigeon, the tortoise, and the frog produced an electrical current. Furthermore, demonstration of the action current of the heart in situ was made by Marey in 1876 and by Waller in 1877, at which time they used the capillary electrometer which Lipman invented in 1873. In 1877 Waller was able to show that the electrical current originating from contraction of the heart spread throughout the body, both in animals and in man, and could thus be recorded on the external surface. Waller was responsible for developing the outline indicating the method of spread which is known to us all.

*Translated by Geoffrey C. P[illegible], M.D., M.R.C.P., [illegible], Hertfordshire, England.
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About the year 1900, Einthoven began to use the capillary electrometer in his research. This apparatus was at that time the most satisfactory known. It was aperiodic but had too great an inertia to permit study of the phenomena observed.

In the address which he gave at Dordrecht in 1893 on new methods of clinical examination, Einthoven pointed out that it was necessary to correct the readings obtained with this apparatus. He demonstrated methods with which correct readings could be obtained and was one of the first to make use of physical and mathematical corrections to give curves identical with those which were obtainable later from more satisfactory apparatus. It was he who in 1893 was the first to show an electrocardiogram illustrating ventricular activity, but only in 1895 was he able to add to this a tracing illustrating contraction of the auricle and the U wave. Until that time the action currents, now recognized for the first time, had been too weak to be registered by the techniques previously employed. It was at this period that he attached the letters P, Q, R, S, T, and U to the different waves which make up the electrocardiogram and thus for the first time brought this terminology into use in this way.

If it is true that the tracings obtained with the capillary electrometer were really representative after correction of the action current, it is also true that the construction of these tracings was difficult for many theoretical and practical reasons.

The Master devoted all his efforts to the construction of an apparatus which would give reliable curves. In this effort he had to overcome many well recognized physical difficulties, for, as he himself said, the apparatus was required to be sensitive to many electrophysiologic changes and at the same time to be capable of numerous changes of direction.

In 1901, in the *Archives Neerlandaises des Sciences Experimentales*, Einthoven described the birth of the string galvanometer in a paper entitled "A New Electrocardiograph."

Again, in 1903, in the *Proceedings of the Koninklijke Academie D'Amsterdam* he made known the first results of the application of this new apparatus in recording cardiac activity in man; the title of his paper was "The String Galvanometer and the Human Heart."

On a second occasion in 1903, he published an article, "Die Galvanometrische Registrierung des menschliches Elektrokardiogramm zugleich eine Beurteilung der Anwendung des Capillär Elektrometers in der Physiologie." This appeared in *Pflüger's Archives fur die gesamte Physiologie*. He said: "I have tried to find a means of avoiding the construction of a new curve which would be a corrected curve if one continued to use the capillary electrometer. After much study I have constructed an apparatus which meets many requirement. It is specially designed to give a direct registration from the human electrocardiogram which will give true readings."

About the same time a galvanometer of similar construction, containing a thread-like conductor lying in a magnetic field, was designed by Ader; this was in 1897. Einthoven has made known, with all his regard for justice and dignity, that he was quite unaware of the construction of this French apparatus when he developed his own string galvanometer. In the series of publications and communications he has made clear to us his lines of thought, the logical sequence of his reasoning, and the mathematical and physical approach to the problem. He gave us, in fact, all the information required for an understanding of the development and the construction of this wonderful instrument which he presented to us. It was in this way that it came so rapidly into use, both in pure science and in clinical and medical studies. It is evident that this apparatus could be used not only for the study of action currents of the heart but also for an understanding of the activity of any organ in which an action current developed. Slight modifications of the apparatus could be made according to type of organ studied, physical characteristics of phenomena analyzed, and research accomplished.

In March, 1912, Einthoven read to the Chelsea Clinical Society his outstanding and famous communication entitled "The Different Forms of the Human Electrocardiogram and Their Significations." On that occasion he propounded the rule which bears his name—$D_{II} = D_I + D_{III}$. This

rule is exact when the points of derivation arise from the apex of any triangle whatever its shape may be. To verify this rule it is necessary to take leads at one and the same time from each of the points involved. Therefore one is obliged to make sure that one has taken readings of the potentials simultaneously from each lead. For the reasons given he developed methods which made it possible to obtain simultaneous inscription of two or more leads. It is difficult, in fact, to obtain with any certainty synchronous points if the leads are registered separately. He developed his concept of the functions of the equilateral triangle. In this concept one assumes that the heart lying in the human body may be considered as the source of punctiform electrical activity situated in the middle of a homogeneous plane which has the shape of an equilateral triangle. From the angles of this triangle (R = R A, L = L A, F = L L) the current is led to the galvanometer. The resultant of the differences in potential may be represented by an arrow which points in a direction controlled at any moment by the contraction of the heart and passing through the central point which represents the heart. This arrow makes an angle α with the R L side of the triangle. In the method employed it is possible to discover at any moment the direction of the manifest resultant of the differences in potential and likewise to estimate the value of the manifest difference in potential of the heart at any moment.

A little later, in 1913, in association with Fahr and De Waart, he published an article which became famous. This appeared in *Pflüger's Archiv für die gesamte Physiologie* and was concerned with the direction, the manifest value of the potentials in the human heart, and the influence of the position of the heart on the shape of the electrocardiogram. In this article he further elucidated the observations made before the Chelsea Clinical Society in 1912 and added some fresh material.

In all of his publications, lectures, and conferences he gave us in a masterly manner his views on the fundamental nature of the phenomena which were illustrated in the electrocardiogram and explained the factors which gave rise to the shape of the electrocardiogram both in health and disease. He made it quite clear that the P wave arises in the auricle and that the Ta wave also derives from the auricle, whereas the complex Q R S and the T wave are related to ventricular activity.

He noted that when the S T interval is isoelectric all the ventricular musculature is in a state of contraction. If this contraction first ceases in the whole ventricular mass no T wave is seen, and should a T wave be found it indicates some asynchronism or a certain degree of asymmetry of ventricular contraction. This occurs when contraction in one part of the ventricles is slightly longer than contraction in the other part.

The essential qualities of the electrical phenomena related to the electrocardiographic tracings were regarded by Einthoven from two different standpoints. In the first theory he considered the heart as an electrical unity so that any activity of the base of the heart would give rise to a negative reading of an electrode at the base and reciprocally. This theory might be described as that of "scattered differences of potential."

But from Lewis' work, which was explained in the Mellon Lecture, it could be shown that an electrode placed on the basal part of the heart could give a negative or a positive reading which depended on stimulation of the basal tissues starting in the former case at the basal side of the tissue and in the latter case at the apical side. This being proved, it was necessary to reconsider the first theory and to avoid speaking of "scattered differences of potential" and to substitute the description "limited differences of potential." Evidently it was not the anatomic position of the excited tissue which controlled the shape of the electrocardiogram, but rather the direction followed by the excitation. It was no longer possible to consider the heart as an electrical unit, and it became necessary to regard it as being made up of a large number of small microscopic structures, each of which was more or less independent. I will give the words used by Einthoven, and it was only after conversations with Sir Thomas Lewis that Einthoven and Lewis came to this conclusion.

In the Mellon Lecture Lewis stated: "I suggested to Einthoven that it was n...

sary to consider the fibres of the myocardium as individual units to make the facts agree with the generally accepted theory of excitation of muscles and nerves In this way the multiplicity of cardiac generators was finally recognized

It is evident that the term manifest which was then used in connection with the size and the resultant of the potentials at any moment was an unfortunate one It is not precise in his determinism It is possible that one ought to take account among other things of the effect caused by the position of the heart in the thorax and to remember that the conducting media are not homogeneous If my memory is correct Einthoven was ready to admit these facts but held them to be relatively unimportant The system which he devised was in a general way quite satisfactory

All the classic works on physiology did not suffice to satisfy Einthoven who believed that the principal reason they existed was to contribute to the betterment of the state of health of mankind by providing a deeper knowledge of physiology and physiopathology He was in contact with physicians and tried at all times to keep them informed of the nature of his work and of the results of his experiments so that new fields of enquiry would be open to them

He brought them into closer association with his work showing them if it were necessary the benefit the patient would derive from this association As proof of this I would like to draw your attention to the fact that electrocardiograms as well as the heart sounds also were recorded from patients in the hospital which was fifteen hundred meters from his laboratory In this case neither the patients nor the apparatus could be moved

It was soon clear to Einthoven that the electrocardiogram of the diseased heart must vary greatly from that of the healthy heart As he himself said a few readings confirmed him in this opinion The number of cases examined was insufficient The most serious cases could not be taken to his laboratory He thought it necessary in the interest of the patient to make an even more profound study of the physiopathology of the heart and to take readings from a larger number of sick persons It was then that Professor Bosscha thought of running electric cables between the hospital and the laboratory fifteen hundred meters away

I would like to make clear once again that the application of research work in the laboratory for the study of disease made continued progress as knowledge in this field increased At no time were the sick absent from Einthoven's thoughts nor was his spirit indifferent to their interests Einthoven was certainly a doctor in the widest sense of the word

His friend Lewis was a man of the same pattern The understanding between them could only be deep and sincere when one bears in mind the intellectual moral and human qualities of these two great men

In 1893 Einthoven had already registered a human electrocardiogram although at that time he had only the capillary electrometer at his disposal Until then only five electrocardiograms from human beings had been registered throughout the world

In 1900 in cooperation with Geluk and Blote he published a work under the title Onderzoek van Lenige Lijders aan Hartzekten met de Capillair Electrometer In 1900 also with the help of K De Lint another of his works appeared entitled Über das normale menschliche Elektrokardiogramma und über die Kapillar elektrometrische untersuchung einiger Herzkranken

He drew our attention to the influence of respiration position of the heart vagal tone the sympathetic nervous system age exertion and the use of certain drugs upon the shape of the electrocardiogram in the healthy subject

He studied various changes in the electrocardiogram caused by right or left hypertrophy by disturbance of conduction between the auricle and the ventricle and also by disordered conduction in the ventricles themselves Furthermore abnormal excitability of the myocardium was investigated as were also auricular nodal and ventricular extrasystoles together with the appearances shown in auricular fibrillation

He also registered electrocardiograms in other disorders and even in congenital disabilities

In his work Einthoven likewise recorded the heart sounds either alone or in association with other tracings

Einthoven was not content to limit the use of the string galvanometer to the registration of electrocardiograms and from 1904 onward he resumed work already started which was designed to register the heart sounds. In collaboration with Flohil and Battaerd he described in 1907 the methods used and the results obtained. The publication bore the title Het Registreren van Menschelijke Harttoonen met de Snaargalvanometer. Some of the recordings described were made at a distance of fifteen hundred meters.

In 1907 working with Wieringa and Snijders he described the third heart sound. It should be noted that in the course of a conference held at Dordrecht in 1893 he had already described the recording of faint sounds particularly in the human and animal heart, which had been detected with the help of the capillary electrometer (linked with this records were made either of the impact at the apex or of the carotid pulse or else tracings were made from a mechanical cardiogram). He had described the most characteristic features. In the course of his investigations he was able to show that stimulation and contraction of the heart occur simultaneously.

The country may be proud to count among its children such a person as Einthoven.

Science rejoices when it is able to honor such men whose discoveries are for the good of humanity and humanity is exalted by their moral and spiritual qualities. It is by the example of such men that the world continues to be beautiful and fruitful. In their modesty they do not think of themselves.

Einthoven
Commemoration address

J. E. Jonkers

On May 21, 1960 it was exactly 100 years since Willem Einthoven was born at Semarang, where his father was assistant municipal physician. We commemorate this fact in gratitude for all that Einthoven has given to the world. You and your colleagues, Mr Chairman, of this International Symposium held under the auspices of the University of Leiden, have all paid tribute to this great scholar by pausing to consider the phenomenal results of science in the field in which Einthoven was a pioneer. In the books *Willem Einthoven* by my colleague A. de Waart and *Helden der Wetenschap* (Heroes of Science) by Dr S. Hoogerwerf I read a fascinating biography of Einthoven. Here we see Einthoven not only as a scholar but also as a person. He was completely lacking in bumptiousness. He was simplicity itself. He was still young when his father died. His sense of responsibility, which even in later years played such an important part in his life, led him, as the eldest son, to support his mother as much as possible. Einthoven was also aware of his shortcomings. He, the gifted scientist, *did not neglect the study of the humanities*. He studied history, music and Latin. He knew by heart whole passages from Cicero's speeches. He enjoyed Horace's poetry, and as a tribute to him the last of the propositions in connection with his thesis was that in order to go through life undisturbed and to achieve something it is necessary *to make the most of one's gifts and one's ability*. Herein, to my mind, lies the secret of his great career as a scientist, quite apart from his particular aptitude. He was persevering and did not let himself be discouraged by opposition and disappointment. He was at the same time a sportsmanlike figure. Sports hardened him and this was also an advantage to him in his career of scientific research. For that matter, sports were responsible for his first scientific publication. When he broke his right wrist in making a grand swing and had a considerable amount of trouble with it, he devoted himself to the study of the various hand and shoulder movements as well as movement of the elbow joints and wrote a number of articles on those subject. He was at the time a medical student. It took him thirty years of diligent work to arrive at a definite theory concerning the electrocardiogram. Famous throughout the world are his string galvanometer and the vacuum string galvanometer, the originals of which are in the Dutch Museum of the History of Science. He also did very useful work in the field of radiotelegraphy. In collaboration with his son, who also had his father's perseverance, he brought about radiographic links with Malabar with the aid of a refined version of the string galvanometer.

Einthoven taught at our university from 1885 until his death. He was a professor at the age of 25. On September 28, 1927 his wife, who had helped him so much during his lifetime and in his career, closed the eyes of her dear husband. A great man went from us then. The world

Prof. Jonkers is Rector Magnificus of Leiden University

honored him in 1924 by awarding him the Nobel prize for physiology and medicine. The Netherlands honored him by making him a Commander in the Order of Oranje Nassau. We honor the man who was an inspiration to so many by laying a wreath at the base of his statue (See Fig. 1.) We are fortunate in having with us today several members of his family. He lies buried at the foot of the peaceful little green church at Oegstgeest, but his inspiring spirit lives on.



Fig. 1. Laying of wreath by the Rector Magnificus of Leiden University, Prof. Dr. J. E. Jonkers, at the bust of Einthoven located in the hall on the second floor of the new physiology building at the Medical School of the University of Leiden. (Foto Bleuzé J. Holvast, Leiden.)

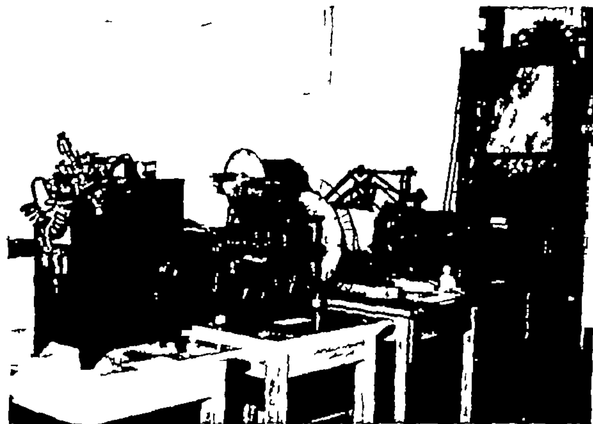


Fig 2 The original electrocardiograph of Einthoven on display the Museum of Science of Leiden (Foto Bleuzé J Holvast Leiden)

After the reception following the Rector s speech many participants went to the Museum of Science to see the original first string galvanometer and other apparatus from Einthoven s laboratory (see Fig 2)

Clinical communications

Atrial septal defect and the mechanism of shunt

George G Rowe M D
Cesar A Castillo M D
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Madison Wis

Over many years there has been much ingenious experimentation and speculation[1] as to the mechanism of production of the shunt in subjects with atrial septal defects The problem has recently been ably reviewed[2] so that it will be reviewed again here only as it applies directly to the discussion The present paper attempts a statistical approach to the mechanism of shunt from data acquired during cardiac catheterization of human subjects with atrial septal defect

Material and methods

From a series of diagnostic catheterizations 24 subjects with atrial septal defects were selected in whom catheterization data included satisfactory pressure records apparently reliable estimations of oxygen saturation in the required areas and in whom no defects were known to exist other than an atrial septal defect No subject who fulfilled the above criteria was excluded from the present analysis

During catheterization children under 12 years of age were anesthetized by rectal anesthesia and adults were awake and without premedication Oxygen saturations were determined by the Waters Conley oximeter which was recalibrated in each patient by the Van Slyke determinations of the oxygen content of systemic and pulmonary arterial blood and which calibration curve is constructed over many months and from many subjects Pressures were measured with Statham strain gauges and recorded on either the Sanborn Poly Viso or the Waters photographic recorder Mean pressures were determined by electrical integration on the Sanborn machine by slow period galvanometers on the Waters recorder and checked by planimetric integration when required or when satisfactory mean pressures were not obtained by the above mentioned methods Oximetric and pressure measurements were done consecutively through the same cardiac catheter and hence depend on the existence of a steady state in order to be compared End diastolic pressures were measured at the point of rapid systolic upsweep on the ventricular pressure tracing and are taken as the average value for each cardiac cycle throughout two respiratory cycles Zero reference point for pressure was taken as the mid point of the anteroposterior chest diameter in the region of the heart Oxygen consumption was

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Table I *Atrial septal defect and shunt*

Catheterization number	Age Sex	Surface Area (M^2)	Heart Rate	Arterial mean pressure (mm Hg)		Systolic pressure (mm Hg)		End-diastolic pressure (mm Hg)	
				Systemic	*Pulmonary*	*LV*	*RV*	*LV*	*RV*
1179	28 F	1 68	80	81	19	103	33	8 9	6 3
1126	36 F	1 46	73	91	61	119	99	9 6	7 0
1159	47 F	1 54	92	155	25	212	45	11 5	8 6
1183	35 F	1 44	100	125	18	160	35	8 7	5 1
1143	7 F	0 91	85	80	18	96	25	8 0	6 3
1125	4 M	0 8?	124	8	24	94	38	9 0	9 0
494	19 M	1 81	64	84	20	114	41	11 5	7 1
609	35 F	1 76	98	87	27	114	46	9 0	7 0
596	28 F	1 54	84	91	15	106	27	9 2	9 4
106	14 M	1 83	83	109	18	105	40	9 2	6 4
885	34 F	1 63	75	93	15	108	33	9 2	7 9
374	25 M	1 92	66	98	20	136	40	16 0	12 6
399	24 M	1 78	92	108	103	118	13?	9	6 6
635	20 F	1 42	76	96	22	105	35	15 8	10 9
1231	4 M	0 71	118	92	12	109	45	9 4	7 5
1232	8 F	1 03	108	91	18	110	30	7 8	4 3
141	9 F	0 89	116	107	14	110	40	8 6	4 5
233	4 M	0 71	178	56	20	96	28	10 9	5 9
382	7 F	0 81	95	87	15	88	29	7 7	2 3
137	9 F	0 76	125	6	141	108	204	2 7	6 1
133	27 F	1 77	77	91	15	106	33	9 1	6 1
663	3 M	0 61	146	72	21	89	36	7 5	6 3
1237	4 F	0 79	106	86	16	112	35	8 8	4 3
1296	36 F	1 47	80	95	69	115	115	8 4	6 6

measured by collecting the expired air in a Tissot spirometer and analyzing the expired gas for oxygen and carbon dioxide by the method of Scholander Indicator dilution curves utilizing indocyanine green dye the Waters Conley cuvette oximeters and recorded on the Waters photographic recorder were an important part of many of the diagnostic studies

Calculation of pulmonary and systemic blood flow and the size of the shunts have been done by standard formulas The oxygen content of mixed venous blood for the purposes of calculation was assumed to equal the oxygen content of superior vena caval blood plus two times the oxygen content of inferior vena caval blood divided by three on the assumption that two thirds of the blood enters the right atrium from the inferior vena cava Pulmonary venous blood was assumed to be 95 per cent saturated unless direct measurement of pulmonary venous blood indicated a higher saturation than this in which case the higher saturation was utilized for calculations Left and right ventricular work were calculated from the standard Starling formula as mean arterial blood pressure times flow Resistances were calculated in centimeter gram second units by the usual formulas

Results

The results are summarized in Tables I and II for the 24 subjects concerned in the main body of the statistical data In 18 subjects for some of whom hemodynamic data are included in this report and in whom the size of the atrial septal defect was determined at operation the r value for the correlation between the size of the defect and the amount of left to right shunt was +0 29 (p > 0 1) The pressure gradient from the left atrium to the right atrium when compared with the left to right shunt indicated a correlation coefficient of −0 04 (p > 0 1) The gradient between the end diastolic pressure of the left and right ventricles when correlated with the shunt indicated a correlation coefficient of +0 38 (p < 0 1) However the left ventricular systolic pressure minus

Atrial mean pressure (mm Hg)		Blood flow index (L/M BSA)		Stroke volume index (ml/BSA)		Ventricular work index (kg M/min/M BSA)		Total peripheral resistance (dynes cm⁻⁵ sec)	Pulmonary vascular resistance (dynes cm sec)
Left	Right	Systemic	Pulmonary	LV	RV	LV	RV		
7 0	6 0	6 0	17 4	75	218	6 6	4 5	6 5	33
6 0	5 0	3 3	5 1	45	0	4 1	4 2	1 507	590
6 7	8 0	3 7	11 4	33	124	6 8	3 9	2 437	83
6 0	6 0	5 1	14 1	51	141	8 6	3 5	1 365	47
6 0	6 0	4 6	7 7	54	91	5 7	1 9	1 504	137
8 0	8 0	4 8	5 4	30	44	5 4	1 8	1 654	289
10 0	5 0	4 6	7 3	72	117	5 3	2 0	66	59
9 2	9 2	3 5	13 8	36	141	4 1	5 1	1 114	59
5 7	5 2	3 0	6 5	36	97	3 7	1 3	1 693	74
6 5	5 7	4 6	17 2	55	207	7 1	5 1	1 061	29
6 0	5 0	3 6	5 6	48	75	4 6	1 3	1 194	79
10 0	8 5	3 2	9 1	48	135	4 3	2 2	1 273	46
4 5	4 5	4 7	1 6	31	17	7 0	2 3	1 013	2 764
9 0	9 0	3 3	10 9	43	89	4 3	5 3	1 633	67
5 7	4 5	5 2	9 3	44	79	6 5	1 3	1 986	76
7 0	5 0	3 6	9 8	33	91	4 5	2 4	1 960	8
2 6	2 9	4 1	8 3	35	72	6 0	1 6	2 344	123
6 2	5 2	5 9	14 8	46	116	4 5	4 0	978	105
5 5	4 8	3 1	7 7	35	63	3 3	1 6	2 7 0	122
5 5	4 5	5 9	4 9	47	39	4 9	9 2	1 110	2 908
5 1	3 1	2 8	10 5	36	136	3 3	2 2	1 498	43
7 5	6 5	6 1	11 4	42	79	6 0	5 7	1 550	190
4 0	4 0	6 9	9 2	65	87	8 1	2 0	1 261	132
4 5	4 0	3 1	1 8	39	23	4 1	1 7	1 610	1 948

the right ventricular systolic pressure correlated more closely with the left to right shunt ($r = +0.61$, $p < 0.001$). The systemic minus pulmonary mean arterial pressure when compared with the shunt indicated an r value of $+0.48$ ($p < 0.02$). There was a significant correlation between the end-diastolic pressures in the left and in the right ventricles ($r = +0.65$, $p < 0.001$); however, there was no correlation between right ventricular end diastolic pressure and the right ventricular stroke index ($r = +0.09$, $p > 0.1$) or between the left ventricular end-diastolic pressure and the left ventricular stroke index ($p < 0.08$, $p > 0.1$). The left ventricular work index minus the right ventricular work index *did not* correlate significantly with the left to right shunt ($r = 0.11$, $p > 0.1$). The systemic minus the pulmonary vascular resistance when correlated with the left to right shunt indicated a correlation coefficient of 0.50 ($p < 0.02$). If an index of distensibility for each ventricle be calculated by dividing its stroke index by its end-diastolic pressure, the difference between these calculated distensibility factors may be related to the *left to right* shunt. When this is done, the r value was found to be $+0.83$ and $p < 0.001$.

Discussion

There is no doubt that on some occasions during heart failure with pulmonary congestion and edema, pulmonary venous blood is desaturated, and under these circumstances calculations based on the assumption that it is fully saturated would indicate a right to left shunt. The inclusion of data from such subjects would vitiate any attempts to relate pressure flow measurements. However, none of the present subjects had pulmonary edema, and right to left shunts have been demonstrated in many compensated subjects with atrial septal defect. Furthermore, it has been stated that in atrial septal defect the pulmonary venous blood may be desaturated from excessive flow alone.[9] Others have doubted that this is a significant factor and have presented data to sh... that pulmonary venous desaturati...

Table II Correlations in subjects with atrial septal defect

	r Value	*p* Value
Related to Shunt		
L → R shunt index with left minus right atrial mean pressure	−0.044	>0.1
L → R shunt index with left minus right ventricular work index	−0.109	>0.1
L → R shunt index with atrial septal defect size	+0.286	>0.1
L → R shunt index with left minus right ventricular end-diastolic pressure	+0.375	<0.1
L → R shunt index with systemic minus pulmonary mean arterial pressure	+0.478	<0.02
L → R shunt index with systemic minus pulmonary vascular resistance	+0.495	<0.0
L → R shunt index with left minus right ventricular systolic pressure	+0.606	<0.001
L → R shunt index with right minus left ventricular distensibility	+0.830	<0.001
General Correlations		
Right ventricular stroke index with right ventricular end-diastolic pressure	+0.087	>0.1
Left ventricular stroke index with left ventricular end-diastolic pressure	+0.080	>0.1
Left with right ventricular end-diastolic pressure	+0.680	<0.001

unusual, and although minor right-to-left shunts may rarely be calculated for this reason, it seems unlikely that this is a common error. Certainly this explanation is unsatisfactory for the right-to-left shunts revealed on indicator-dilution curves. The presence of streaming of blood in the right atrium is undoubted, and it has been shown that in general blood from the inferior vena cava tends more to cross an atrial septal defect than does that from the superior vena cava. The demonstration of such streams, their direction of flow, and the fact that dye contained in them may cross the septum still, however, does not answer the basic hemodynamic question of the determinants of flow through the defect. The postulate that the relative atrial positions determine the flow of blood through the septal defect seems to have been disproved by the demonstration that change of position of the atria by placing the subject in head-down tilt fails to eliminate the shunt.[1]

The absence in the present series of a significant correlation between the size of the atrial septal defect as measured at operation and the amount of shunt is expected and has been discussed by others.[4, 12] Indeed, if the patients in whom the shunt was reversed were subjected to operation, the present correlation would be even less, since it is well known that the predominant shunt may be in either direction. It should be emphasized that measurement and comparison of atrial mean pressures is difficult because (1) the pressure is small and small errors are magnified percentagewise, (2) pressure varies considerably with respiration as well as cardiac action, and (3) the pressures in the two atria have not been measured simultaneously. There seems no doubt that if the atrial septal defect is sufficiently small, its size will limit the shunt, and under these circumstances a considerable pressure gradient may be measured across the defect. This gradient may even reach the normal interatrial gradient.[2, 7] In those with larger defects, such as are known to exist in many of the present subjects, the mean pressure gradient between the left and right atria is very small, as was postulated by Barger and associates, and in the present series does not correlate with the size of shunt. The present authors accept the fact that in order for blood flow to occur through an orifice (such as an atrial septal defect) there must be a pressure gradient across the orifice; however, from the present data this gradient seems to be so small that it has not been measured sufficiently accurately to be demonstrated. Other investigators have had a similar lack of success in their endeavors to relate left and right atrial pressures to the shunt between the two atrial cavities,[4, 7, 12] and some have emphasized transient pressure gradients which cause significant shunting but are not reflected adequately in the mean left and right atrial pressures.[4] Although it is stated that Calazel and others[11] found a good correlation between the left and right atrial pressures and the direction of the shunt, study of their paper reveals that of the 9 cases reported only two had

an uncomplicated atrial septal defect Two had only a patent foramen ovale in which presumably no left to right interatrial shunt occurs The other cases had pulmonic stenosis tricuspid atresia mitral stenosis and transposition of the great vessels so that it is doubtful whether data derived from such subjects may be applied to the problem under discussion The data from animals with experimental atrial septal defects indicate that, even when a gradient can be measured between the atria it exists only as long as the heart continues functioning and vanishes when cardiac arrest is induced [3] Hence, the primary driving force of the interatrial shunt resides in some phase of cardiac activity

Unfortunately the measurement and comparison of ventricular end-diastolic pressures are among the least accurate in any study This is partly because the pressure levels and differences involved are so small that a small error becomes magnified percentagewise and partly because the exact point at which an end diastolic pressure should be measured on the curving junction of systole and diastole on a ventricular pressure curve becomes a matter of opinion In the present study these were all measured and rechecked by the same individual so as to secure greater uniformity Still complete accuracy remains unobtainable It is of some interest that the end diastolic pressures in the two ventricles correlate so closely ($r = +0.68$) with each other Presumably this is because venous pressure on each side of the heart equilibrates through the interatrial defect The difference between the end-diastolic pressures of the two ventricles failed to correlate well with the shunt indicating that again the study of pressure alone is probably inadequate to explain the shunt

It has been postulated [1,4] that a sizable defect between the two atrial chambers reduces them to a common chamber and that the proportions of flow out of this common chamber are determined by which ventricle is most easily filled Or in other words the diastolic distensibility of the ventricles determines the size of shunt This appears to be confirmed by the present data ($r = +0.83$) A logical extension of this postulate is that the ventricular systolic pressures the mean arterial pressures and the systemic and pulmonary vascular resistances are related to the size of the shunt because they help to determine the thickness of the ventricular walls and therefore their distensibility The statistical relation between the ventricular distensibility and the shunt must be considered in light of the fact that any calculation of distensibility of a ventricle must include its stroke volume The calculated distensibility is therefore mathematically related to the shunt and a portion of the correlation between the shunt and the calculated distensibility of the ventricles is spurious It should also be pointed out that to whatever extent the resistance to flow at the atrial septal defect limits flow the correlation between ventricular distensibility and shunt will be reduced Nevertheless when all these factors are considered it seems reasonable that the calculated relation between ventricular distensibility and the shunt is significant

Conclusions

1 A statistical study is presented of 24 subjects in whom an atrial septal defect and no other defect was demonstrated at cardiac catheterization

2 The various parameters related to the left to right shunt in line of descending order of correlation between measured or calculated parameter and shunt are the following (a) right ventricular as compared to left ventricular distensibility (b) left ventricular minus right ventricular systolic pressure (c) systemic minus pulmonary vascular resistance (d) systemic minus pulmonary mean arterial pressure

3 The degree of mathematical relation between some of these parameters requires that allowance be made for spurious mathematical correlation

REFERENCES

1 Uhley M H Lutembacher's syndrome and new concept of the dynamics of interatrial septal defect Am Heart J 24:315 1942
2 Little R C Opdyke D F and Hawley J G Dynamics of experimental atrial septal defects Am J Physiol 158 241 1949
3 Martin R B and Essex, H E Experimental production and closure of atrial septal defects with observations of physiologic effects Surgery 30 283 1951

4 Swan H J C Burchell H B and Wood E H The presence of encoarteral shunts in patients with interatrial communications Circulation 10 705 1954
5 Bedford D E I pp C and Parkinson J Atrial septal defect Brit Heart J 3:37 1941
6 Cournand A Motley H L Himmelstein A Dresdale D and Baldwin J Recording of blood pressure from the left auricle and the pulmonary veins in human subjects with interauricular septal defects *Am J Physiol* 150 267 1947
7 Dexter L Atrial septal defect Brit Heart J 18 209 1956
8 Handelsman J C Bing R J Campbell J A *and Griswold H E Physiological studies* in congenital heart disease V The circulation in isolated septal defects Bull Johns Hopkins Hosp 82:615 1948
9 Limon Lason R Cardiovascular M Puech I De L Cruz M A Rubio V Bouchard F and Son J El cateterismo intracardiaco V La communicación interauricular correlación de los hallazgos hemodinamicos con los datos embriológicos clinicos radiologicos y electrocardiográficos en 50 casos Arch Inst cardiol Mexico 23:279 1953
10 Wood P Pulmonary hypertension Brit M Bull 8:318 1951 2
11 Lind J and Wegelius C Atrial septal defects in children Circulation 7:819 1953
12 Brannon E S Weens H S and Warren J V Atrial septal defect study of hemodynamics by technique of right heart catheterization Am J M Sc 210 480 1945
13 Selzer A and Lewis A E The occurrence of chronic cyanosis in cases of atrial septal defect *Am J M Sc 218:516 1949*
14 Barger J D Edwards J E Parker R L and Dry T J Atrial septal defect presentation of a case with obstructive pulmonary vascular lesions caused by metastatic carcinoma *Proc Staff Meet Mayo Clin 23:182 1948*
15 Dow J W and Dexter L Circulatory dynamics in atrial septal defect J Clin Invest 29:809 1950 (Abstract)
16 Calazel P Gerard R Daley R Draper A Foster J and Bing R J Physiological studies in congenital heart disease XI A comparison of the right and left auricular capillary and pulmonary artery pressures in one patient with auricular septal defect Bull Johns Hopkins Hosp 88 20 1951

Urinary excretion of catecholamines and their metabolites in pheochromocytoma

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In recent years it has been established that the major urinary metabolites of circulating epinephrine (E) and norepinephrine (NE) are 3-methoxy-4-hydroxymandelic acid (MOMA) and the respective 3-methoxy amines, metanephrine (MN) and normetanephrine (NMN). Since these metabolites appear in the urine in much larger amounts than the parent amines, convenient methods for their determination should be of value in the diagnosis of pheochromocytoma. Current interest is centered chiefly on the determination of MOMA, the major urinary metabolite of infused catecholamines. Although most of the methods for assaying this compound seem to have little technical advantage over the determination of free catecholamines, at least two simplified procedures for the detecting of an increased excretion of MOMA have been described.[1-4] Marked elevations of the excretion of MOMA in cases of pheochromocytoma have been demonstrated with each of these methods. It has not been established, however, that urinary MOMA is actually a more reliable index than the free catecholamines in distinguishing patients with pheochromocytoma from the remainder of the hypertensive population.

Recently, spectrophotometric methods for the determination of urinary MOMA[4] and for the assay of total metanephrines (NMN plus MN) have been developed in this laboratory. Measurements of these metabolites, as well as the urinary catecholamines, have now been performed in a large number of patients with essential hypertension and in 23 patients with pheochromocytoma. The present report describes the accuracy with which each of these three indices of catecholamine production—the free catecholamine excretion (NE plus E), the total metanephrine excretion (NMN plus MN), and the MOMA excretion—served to detect pheochromocytoma in this series of patients. Since in our experience the assay of total metanephrines has been the most convenient method for screening purposes, certain aspects of this procedure are considered in detail.

Methods

Twenty-four hour specimens of urine were collected in 10-15 ml. of 6N hydrochloric acid and stored at 0°C. Specimens from 2 of the patients with pheochromocytoma (Cases 2 and 9) were in storage for 48 months prior to the time of complete assay, but the remainder of the specimens

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were stored for 30 months or less. NE and E have been found to be stable under these conditions for at least 4 years and the methylated metabolites for at least 1 year, these being the longest time periods tested to date. MOMA has been reported to be stable in urine for many months under similar conditions.

Free catecholamines were determined by a modification of the trihydroxyindole method using iodine as the oxidizing agent.[19] Both NE and E were measured in all specimens from patients with pheochromocytoma, but the values to be reported are for combined NE plus E. These values are not corrected for an average 87 per cent recovery.

Total urinary metanephrines (free plus conjugated NMN plus MN) were determined essentially by the method of Pisano with several minor alterations. The modified procedure is as follows. An aliquot of urine equivalent to 0.5 per cent of the 24 hour volume (4-15 ml.) is added to a 40 ml. centrifuge tube and acidified with 0.1 volume of 2N hydrochloric acid, giving a final pH of less than 1. The tube is placed in a bath of boiling water for 20 minutes to hydrolyze conjugated NMN and MN. After cooling, two drops of 0.1 per cent bromcresol purple are added as an indicator and the pH is adjusted to 6.0-6.5 with 1N sodium hydroxide. The sample is diluted to 30 ml. with distilled water and any sediment is removed by centrifugation. The supernatant urine is passed over a 1.2 by 5-cm. column of Amberlite CG 50* buffered at pH 6.5 as described previously. The flow rate must not exceed 1 ml. per minute. The column is then washed with 20 ml. of deionized water and eluted with 10.0 ml. of 4N ammonium hydroxide. To a 4.0 ml. aliquot of the ammonium eluate is added 0.1 ml. of 1.6 per cent sodium metaperiodate; this cleaves the side chain of both NMN and MN to yield vanillin. After 2 minutes, 0.1 ml. of 10 per cent sodium bisulfite is added to remove excess periodate ion. To a second 4.0 ml. portion of the eluate, which serves as a urine blank, is added 0.1 ml. of water and 0.1 ml. of 10 per cent sodium bisulfite. The amount of vanillin formed by periodate treatment is determined by measuring the optical density (O.D.) of the sample at 360 mμ with the spectrophotometer adjusted to zero O.D. with the urine blank. Under these conditions, samples of normal urine measured with a 1.0 cm. light path have an O.D. at 360 mμ of 0.070 or less. On the basis of the O.D. of standard solutions and the constant fraction of the daily urine volume assayed (0.5 per cent), a factor can be calculated for the direct conversion of the *O.D. reading to total metanephrine excretion*. On our instrument (Beckman DU spectrophotometer) total metanephrine excretion in milligrams per day of NMN equivalents (entire reading assumed to be due to NMN) is 18.8 × O.D. at 360 mμ. No correction is made for an average recovery of 84 per cent.

The absorption peak of vanillin formed in the assay of total metanephrines is at 347 mμ, but many samples of urine from patients without pheochromocytoma contain an unidentified material with an absorption peak at 333 mμ. The contribution of this interfering material to total absorbency at the vanillin peak of 347 mμ is often quite significant. Therefore, the sample is read at 360 mμ, where the absorbency of vanillin is 80 per cent of its peak value but that of the 333 mμ absorbing material is minimal. Every value over 1.0 mg. per day (O.D. at 360 mμ over 0.053) in patients without pheochromocytoma has been due to the presence of unusually large amounts of this 333 mμ absorbing material. For this reason all samples with an O.D. at 360 mμ greater than 0.053 are also read at 347 mμ and 333 mμ to determine whether the high reading is due to this interfering substance (peak at 333 mμ) or to vanillin (peak at 347 mμ). All patients with pheochromocytoma have had the typical vanillin peak of 347 mμ. Because of this interfering material and the low O.D. values in samples from patients without pheochromocytoma, the method should be considered quantitative only for excretion values higher than 2.0 mg. per day of NMN equivalents.

Urinary MOMA was determined as described in a separate communication.[21] In brief, the phenolic acids are extracted from a salt-saturated acidified aliquot of

*Amberlite CG-50, Type 2 200 mesh and ... Rohm & Haas Company, Fair Lawn, N. J.

urine with ethyl acetate and returned to a small portion of 1M potassium carbonate The MOMA in this extract is then converted to vanillin with periodate After adjustment of the extract to pH 7 5 the vanillin is extracted into toluene and returned to 1M potassium carbonate The O D at 360 mμ of the carbonate layer is then determined as in the procedure for total metanephrines The recovery of added MOMA is quantitative

Results

Patients without pheochromocytoma In a series of 114 hypertensive patients who were not acutely ill the excretion of free catecholamines (NL plus E) was found to be 32 ± 18 μg per day (mean ± S D) The upper limit of normal for the ambulant hypertensive population is considered to be 100 μg per day Only 2 hypertensive patients without pheochromocytoma have been encountered with values above this figure their excretions of free catecholamines were 115 and 117 μg per day respectively

In a second series of 121 patients (91 with primary hypertension and 30 without hypertension) the excretion of total metanephrines (NMN plus MN) was 0 62 ± 0 28 mg per day of NMN equivalents (mean ± S D) No statistically significant difference was found between the hypertensive and nonhypertensive groups but the semiquantitative nature of the assay in this range makes this observation of questionable significance The upper limit of normal for the excretion of total metanephrines is considered to be 1 3 mg per day Every value above 1 0 mg per day including those of 3 patients who had excretion figures considerably higher than those of the rest of the population (values of 1 6 1 6 and 1 7 mg per day) was due to the presence of an unidentified but easily recognizable substance which interfered with the determination (see Methods) No drugs were encountered which directly interfere with the assay The ingestion of bananas previously shown to increase the urinary excretion of conjugated catecholamines did not influence the excretion of the total metanephrines Treatment of hypertensive patients with monoamine oxidase inhibitors however may increase the excretion values to levels as high as 2 2 mg per day This increase may persist to some degree for as long as 2 weeks after the enzyme inhibitor is discontinued

In a series of 20 patients with primary hypertension the excretion of MOMA was found to be 3 7 ± 1 1 mg per day (mean ± S D) The upper limit of the normal range for hypertensive patients is considered to be 6 0 mg per day one patient had a value above this figure (7 1 mg per day)

Patients with pheochromocytoma In each of the 23 patients with pheochromocytoma MOMA was the major metabolite excreted in the urine total metanephrines were next most prominent and the free catecholamines comprised only a small fraction of the total excretion Since the clearest indication of an abnormally high excretion value for a compound is the degree of elevation above normal rather than the absolute excretion in milligrams the result in each patient is expressed as a multiple of the upper limit of normal for each assay As shown in Figs 1 and 2 two types of patterns of excretion were observed In the first group (15 patients Fig 1) the relative increase above normal was greatest for the free catecholamines next greatest for the total metanephrines and least for MOMA This pattern was relatively constant over a wide range of values In the second group (8 patients Fig 2) the methylated metabolites were increased relative to normal more than the free catecholamines the over all pattern from patient to patient was more variable than in the first group

From a consideration of the two groups as a whole the comparative value of the three different assays in detecting the presence of a tumor may be summarized as follows (1) A diagnostic elevation of all three indices of catecholamine production was found in 20 of the 23 patients (2) In the patients who did not have a diagnostic increase in urinary excretion by all three tests (Cases 1 2 and 4) the assay of free catecholamines was the only test which was diagnostic in all 3 patients (3) The single test giving the largest relative increase over normal was either the assay of free catecholamines or the determinati[illegible] of total metanephrines depending

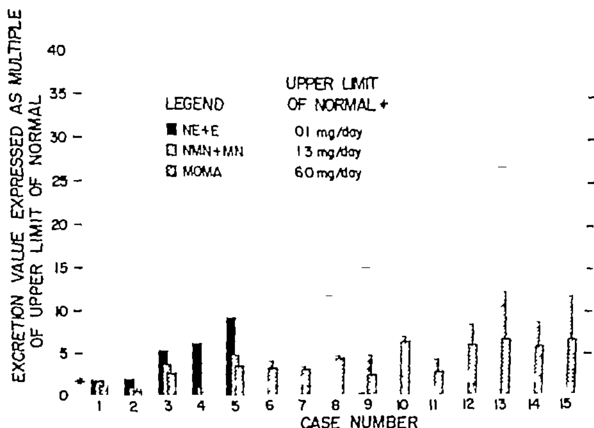


Fig. 1. Pattern of excretion of urinary catecholamines and metabolites in 15 patients in whom the free catecholamines showed the greatest relative increase over the upper limit of normal (see text). The horizontal line marked with an asterisk represents the upper limit of normal for each assay. *NE + E*, Free catecholamines. *NMN + MN*, Total metanephrines. *MOMA*, 3-methoxy-4-hydroxymandelic acid.

the pattern of excretion of the patient (Fig. 1 vs. Fig. 2).

Discussion

The findings of this study indicate that the determination of the free catecholamines or either of their major metabolites in urine provides an excellent chemical basis for the diagnosis of pheochromocytoma in most cases of the disease. This does not imply that each assay is of equal validity in an individual case. In one type of patient (Fig. 1) the determination of free catecholamines shows the greatest relative increase over normal. This assay is of particular value in patients with minimally secreting tumors (Cases 1-4). In the second type of patient (Fig. 2) the excretion of total metanephrines shows the largest relative elevation. Our interpretation is that considerable quantities of catecholamines are being methylated directly in the tumor in the latter group of patients. The relative excess of methylated metabolites in the urine could thus arise from a tumor which is releasing a mixture of catecholamines and metabolites into the blood stream. The pattern of excretion of the first group, on the other hand, is believed to be the result of the release of relatively pure catecholamines from the tumor. Previous work from this laboratory[14] demonstrating that pheochromocytomas may contain both NMN and catechol O-methyl transferase is compatible with the postulate that considerable metabolism of the catecholamines may occur directly in the tumor prior to their release into the circulation.

The determination of urinary MOMA might seem a priori to be the ideal chemical method of detecting patients with pheochromocytoma. However, the high range of normal for the excretion of this compound (up to 6 mg. per day) more than offsets the advantage of its being the major

urinary metabolite. Two cases in the literature are reported to have shown an increased excretion of MOMA at the time at which the value for free catecholamines was normal (Patient 23, Table III, in the series of Gitlow and associates, and the patient described by Kraupp and associates[9]). It is quite possible that these patients were of the type shown in Fig. 2. If this is true, a determination of total metanephrines should have been at least as helpful as the MOMA excretion in establishing the diagnosis.

Because of its high degree of reliability and comparative ease of technical performance, the determination of total metanephrines is favored by us for the screening of hypertensive patients for the presence of pheochromocytoma. When the results by this test are equivocal, an assay of free catecholamines is indicated. On the basis of these general concepts, the following approach to diagnosis has been adopted in our laboratory.

1. A determination of total metanephrines is performed as part of the initial laboratory examination of each hypertensive patient. The phentolamine (Regitine) test,[17] formerly employed as a screening procedure, is no longer used. An excretion of total

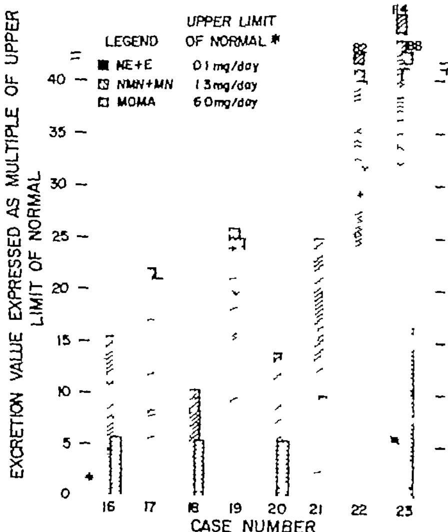


Fig. 2. Pattern of urinary excretion in 8 patients in whom O-methylated metabolites showed the greatest relative increase over normal.

metanephrines of 1 0 mg per day of NMN equivalents or less in a patient with sustained hypertension is considered to rule out pheochromocytoma whereas a value of 2 5 mg per day or higher for total metanephrines is considered to be diagnostic of pheochromocytoma

2 Values between 1 0 and 2 5 mg per day of NMN equivalents (6 per cent of patients without tumors in this series) are considered equivocal This rather wide equivocal range is selected to minimize the chance of both false positive and false negative diagnoses If the U V spectrum is characteristic of vanillin (peak at 347 mμ see Methods) or the value is over 1 3 mg per day regardless of the U V spectrum a determination of free catecholamines is performed If the U V spectrum indicates the presence of interfering material (peak at 333 mμ) and the value is between 1 0 and 1 3 mg per day the free urinary catecholamines are determined only on strong clinical suspicion of pheochromocytoma

3 In the patient with paroxysmal hypertension who has a normal excretion of total metanephrines and little or no elevation of blood pressure on the day on which the urine is collected a timed specimen of urine is collected during a spontaneous paroxysm or after a histamine test[19] and assayed for free NE and E Failure to demonstrate an increase in the excretion of free catecholamines during an elevation of blood pressure is considered to rule out pheochromocytoma Conversely a clear increase (at least twofold) in the excretion of either NE or E at this time supports the diagnosis

The foregoing diagnostic approach has been followed for about one year During this time samples of urine from approximately 150 hypertensive patients who were clinically suspected of having pheochromocytoma have been studied and 10 cases of the disease have been proved No known false positive or false negative diagnoses have occurred in this series of patients

In most hypertensive patients, chemical tests of the urine clearly indicate the presence or absence of pheochromocytoma The greatest diagnostic challenge is the rare patient with paroxysmal hypertension whose excretion values are increased only at the time of an attack or the occasional patient with persistent hypertension who has only a borderline increase in the excretion of catecholamines or their metabolites In such patients the clinical picture and the results of pharmacologic tests as well as the urinary excretion data must be carefully considered in arriving at a diagnosis

Summary

Twenty four hour specimens of urine from 23 patients with pheochromocytoma and a large group of hypertensive subjects were assayed for free catecholamines (norepinephrine plus epinephrine) total metanephrines (metanephrine plus normetanephrine) and 3 methoxy 4 hydroxymandelic acid Twenty of the 23 patients with tumors had a diagnostic increase in the urinary excretion of all catecholamine metabolites In the other 3 patients the assay of free catecholamines was the single most reliable test Because of its over all reliability and ease of performance the assay of total metanephrines is favored for screening hypertensive patients for the presence of pheochromocytoma In the occasional patient whose value is equivocal by this assay the determination of free catecholamines is considered to be the most helpful test in confirming or excluding the diagnosis

We wish to acknowledge the excellent technical assistance of Miss Doris Watts in this study

REFERENCES

1 Armstrong M D McMillan A and Shaw K N F 3 methoxy 4 hydroxy D mandelic acid urinary metabolite of norepinephrine Biochim et biophys acta 25 422 1957
2 LaBrosse E H Axelrod J and Kety S C O methylation the principal route of metabolism of epinephrine in man Science 128 593 1958
3 Goodall McC Kirshner N and Rosen L Metabolism of noradrenaline in the human J Clin Invest 38 707 1959
4 Gitlow S E Mendlowitz M Khassis S Cohen G and Sha J The diagnosis of pheochromocytoma by determination of urinary 3 methoxy 4 hydroxymandelic acid J Clin Invest 39 221 1960
5 Studnitz W V and Hanson A Determination of 3 methoxy 4 hydroxymandelic acid in urine by high voltage paper electrophoresis Scandinav J Clin & Lab Invest 11 101 1959
6 Weise V K McDonald R K and LaBrosse E H Determination of urinary 3 methoxy 4 hydroxymandelic acid in man Fed Proc 19 294 1960

7 Sandler M and Ruthven C R J Quantitative colorimetric method for estimation of 3 methoxy 4-hydroxy mandelic acid in urine Value in diagnosis of phaeochromocytoma Lancet 2 114 1959

8 Sandler M and Ruthven C R J Colorimetric estimation of 3 methoxy-4 hydroxy mandelic acid in urine Lancet 2 1034 1959

9 Gitlow S E Ornstein L Mendlowitz M Khassis S and Kruk E A simple colorimetric urine test for pheochromocytoma Am J Med 28 921 1960

10 Hycel Pheo et Booklet 3 methoxy-4 hydroxy mandelic acid determinations Houston Texas 1960 Hycel Inc.

11 Pisano J J Crout J R and Abraham D Determination of 3 methoxy-4-hydroxy mandelic acid in urine (I preparation)

12 Pisano J J A simple analysis for normetanephrine and metanephrine in urine Clin Chim Acta 5 406 1960

13 Crout J R Standard methods of clinical chemistry Vol III New York 1960 Academic Press

14 Crout J R and Sjoerdsma A The clinical and laboratory significance of serotonin and catecholamines in bananas New England J Med 261 23 1959

15 Sjoerdsma A King W M Leeper L C and Udenfriend S Demonstration of the 3 methoxy analog of norepinephrine in man Science 127 876 1958

16 Kraupp O Stormann H Bernheimer H and Obenau H Presence and diagnostic significance of phenolic acids in urine in pheochromocytoma Klin Wchnschr 3 76 1959

17 Emlet J R Grimson K S Bell D M and Orgain E S Use of piperoxan and Regitine as routine tests in patients with hypertension J A M A 146 1383 1951

18 Roth G M and Kvale W F A tentative test for pheochromocytoma Am J M Sc 210 653 1945

Surgical implications of single coronary artery
A review and two case reports

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Single coronary artery is a rare anomaly which usually is of no clinical significance.[4] In cardiac operations, however, the recognition of this anomaly may be of crucial importance. The present study describes the anatomic variants of single coronary artery with emphasis on surgical implications. The literature is summarized since the publication of Smith's collective review in 1950, and two case reports are added.

Case reports

Case 1. A premature Negro female infant was delivered by cesarean section on Jan. 15, 1958. Her condition remained satisfactory until January 23, when poor feeding and lethargy were noted. On January 25 she developed respiratory distress, edema, and cyanosis. She did not respond to medical therapy and died on January 26.

At autopsy the cause of death was attributed to congenital heart disease with cardiac failure, bilateral pleural effusion, and encephalomalacia of the thalamus. Examination of the heart revealed cardiomegaly and a large ventricular septal defect. *Microscopic examination of the heart demonstrated* marked edema of the myocardium. There was a single ostium where the left coronary ostium normally is situated (Fig. 1). The single coronary artery divided into two main branches 2 mm. from the orifice. The left branch followed the course of a normal left coronary artery, giving rise to the anterior descending branch and terminating as the circumflex branch. The right main trunk traveled the course of a normal right coronary artery and terminated as the posterior descending branch. An unusually large infundibular branch crossed diagonally from right to left across the outflow tract of the hypertrophied right ventricle.

Case 2. A Negro male infant, one of a pair of twins, was born on May 2, 1956. Both of the *infants were discharged from the hospital on May 25.* On June 3 the infant refused to nurse, and the following day his breathing became labored. He was rushed to the hospital but was dead on arrival.

At autopsy the cause of death was attributed to congenital malformation of the heart, pulmonary congestion, and atelectasis. Examination of the heart revealed hypertrophy of the right ventricle, hypoplasia of the mitral valve, and dilatation of the pulmonary artery. The aorta was hypoplastic and stenotic. There was marked stenosis of the aortic valve, and only two cusps, anterior and posterior, were present. A single coronary artery ostium was located at the posterior cusp (Fig. 2). Arising from the ostium was a single coronary trunk which coursed around the left atrioventricular groove and continued to the right atrioventricular groove. Here its terminal branches coursed over the preventricular surface of the right ventricle. Anterior and posterior descending branches and marginal branches arose in a normal pattern of distribution.

Discussion

By definition, a single coronary artery arises by one ostium from an arterial trunk and nourishes the entire myocardium re-

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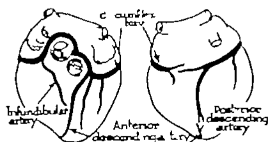


Fig. 1 Drawing of coronary distribution in Case 1. The single coronary artery arises at the usual site of origin of the left coronary artery. The branch supplying the right heart passes behind the aorta. An hypertrophied infundibular branch arises from the right coronary artery.

gardless of the distribution of the branches. Smith[17] in 1950 found 45 cases in his review of the literature. He classified these into three anatomic types: *Type 1*. A single coronary follows the course of only the normal right or left coronary artery. *Type 2*. A single coronary artery arises from one ostium but divides so that branches are present in the distribution of both the right and left coronary arteries. *Type 3*. A single coronary artery has so atypical a distribution that it cannot be compared with the right or left coronary artery. The latter type had been described previously by Krumbhaar and Ehrich. Smith also included in this third group those cases in which insufficient data were given. We have designated such cases as *Type 4*.

The present review adds 25 new cases bringing the total to 70 cases of single coronary artery. Data on the cases reported since 1950 are presented in Table I.

Several mechanisms of development of this anomaly have been presented.[n] It is generally agreed that a single coronary artery is the result of one of two developmental anomalies: (1) absence of a coronary artery anlage (Type 1) or (2) misplacement with fusing of the coronary artery anlagen (Type 2).

The presence of a single coronary artery in congenitally malformed hearts may present a considerable problem during open heart operation. Recent reports have appeared on the accidental division of an anomalous single coronary artery during ventriculotomy for the correction of tetralogy of Fallot. Kirklin reported a case in which an unrecognized left coronary artery arose from a single right coronary artery and crossed the outflow tract of the right ventricle. This branch was divided during the ventriculotomy. Senning[18] reported a case in which the entire left coronary artery arose from the right coronary artery and crossed the region of the infundibular stenosis. This branch was divided during the right ventriculotomy. Friedman's[4] case was similar to those of Kirklin and Senning (Fig. 3). The left coronary artery was divided when the incision was made in the right ventricle. In all three cases the patients died immediately upon division of the left coronary artery. These three cases are examples of Type 2 single coronary artery, the left coronary artery arising from a single right coronary artery.

In the majority of cases with this anomaly the distribution of major coronary vessels is such that the usual type of incision may be made with impunity. However, in a few instances a major branch crosses in front of the pulmonary artery and

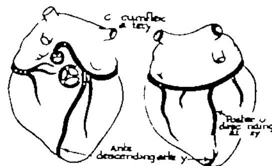


Fig. 2 Drawing of the coronary distribution in Case 2. The single vessel arises from an aortic sinus, encircles the heart from left to right, and supplies the entire myocardium.

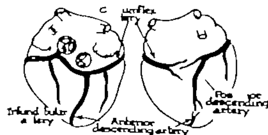


Fig. 3 Drawing of single coronary artery distribution with major vessel passing in front of the pulmonary artery. The usual incision of right ventricular outflow tract and pulmonary artery would result division of this vessel.

Table I. Twenty-five cases of single coronary artery reported in the literature since 1950

Number	Age	Sex	Single artery present	Weight of heart (grams)	Type*	Autopsy	Year	Author
1	9 days	M	R		4	CHD	1956	Alexander (Case 5)
2	11 days	F	L	—	2	VSD	1960	Longenecker et al
3	14 days	M	L	—	1	Hypoplasia of mitral and aortic stenosis bicuspid aortic valve	1960	Longenecker et al
4	7 wk.	F	R	54	3	Coarctation of right pulmonary artery and aorta bicuspid aortic valve	1959	Raekallio
5	4½ mo.	F	R	—	2	Transposed great vessels to right ventricle	195[illegible]	Edwards et al
6	7 mo.	F	—	50	3	Transposition of great vessels	1939	Harris and Farber (Case 6)
7	1 yr.	M		90	3	Transposition of great vessels	1939	Harris and Farber (Case 12)
8	22 mo.	—	R	—	2	Tetralogy of Fallot accidental division of left coronary artery during ventriculotomy	1959	Kirklin
9	Child	—	R	—	1	Tetralogy of Fallot accidental division of left coronary artery during ventriculotomy	1959	Senning
10	Child	—	L	—	1	Transposition of great vessels	1958	Keith
11	6 yr.	F	R	190	2	Tetralogy of Fallot absent left pulmonary artery and pulmonary valve accidental division of left coronary artery during ventriculotomy	1960	Friedman

*Modification of Smith classification (see text).

would be divided by an incision in the right ventricular outflow tract extending into the pulmonary artery. The presence of a major coronary vessel may not always be appreciated from inspection at the operating table. In such cases, temporary occlusion of the area including the upper portion of the outflow tract and the base of the pulmonary artery may indicate the presence of a major coronary vessel. In these circumstances, correction of the pulmonic stenosis might be accomplished by resection of the hypertrophied infundibulum and opening of the valve commissures without division of the annulus.

Summary and conclusions

1. A total of 70 cases of single coronary artery have been reported, including the two new cases added in this review.

Table I —(Cont'd)

Number	Age	Sex	Single artery present	Weight of heart (grams)	Type	Autopsy	Year	Author
12	21 yr	M	R	—	2	Myocardial ischemia after exertion	195	Nicod (Case 1)
13	40 y	M	R	—	4	Thyrotoxicosis	1956	Alexander[1] (Case 2)
14	41 yr	F	R	460	2	Myocardial infarct	1954	Swan and Fitzpatrick[17]
15	44 yr	F	R	255	2	Malignant lymphoma	1939	Staples and Edwards[15] (Case 2)
16	49 y	F	R	320	1	Hemothorax due t auto accident	1950	Dutra[3]
17	51 y	M	L	—	4	SBE	1956	Alexander[1] (Case 4)
18	56 yr	M	L	460	2	F tty infiltration of liver	1956	Dent and Fisher[2] (Case 2)
19	64 yr	M	R	—	2	M ocardial infarct	1956	Dent and Fisher[2] (Case 1)
20	74 yr	M	L	—	4	M ocardial infarct	1956	Alexander[1] (Case 3)
21	7 yr	M	L	325	1	Ca esophagus	1939	Staples and Edward (Case 1)
22	77 yr	M	R	41	2	—	195	Nicod (Case 2)
3	9 yr	M	L	575	1	Auricular and entricular infarction	1959	Tremouroux et al[20]
24	82 yr	F	L	—	4	Pulmonary embolism	1956	Alexander[1] (Case 1)
5	83 yr	F	L	950	1	CVA CHF	1954	Plachta and Speer[14]

Modification of Smith classification (see)

2 In the majority of cases of single coronary artery the distribution of major vessels is such that a standard right ventriculotomy extending into the pulmonary artery may be made with impunity

3 In a few cases a major vessel passes in front of the pulmonary artery The presence of such an artery is not always apparent on inspection at the operating table but temporary occlusion of the area of the annulus prior to division may indicate the presence of such a vessel

REFERENCES

1 Alexander R W and Griffith G C Anomalies of the coronary arteries and their clinical significance Circulation 14 800 1956
2 Dent E DuBose J and F her R S Single coronary artery report of tw cases Ann I t Med 44 10 4 1956
3 Dutra F R Anomalies of coronary arteries Arch I t Med 85 955 1950

4 Edwards J F Anomalous coronary arteries with special reference to arteriovenous like communications Circulation 17 1001 1958
5 Edwards J E James J W and DuShane J W Congenital malformation of the heart Lab I t 1 197 1952
6 Friedman S Ash R Klein D and Johnson J Anomalous single oronary rtery complicating ventriculotomy in ch ld w th cyanotic congenital heart di ease Am Heart J 59 140 1960
7 Harris J S and Farber S Transpos tion of the great cardiac essels w th speci l ref rence to the phylogenetic theory of Spitzer Arch Path 28:42 1939
8 Keith J D Rowe R D and Vlad P Heart disease in infancy nd childhood New York 1959 The Macmillan Company
9 Kirklin J W Ellis F H Jr McGoon D C DuShane J W nd Swa H J C Surgical treatment for tetralogy of Fallot by open intra ardiac repair J Thoracic Surg 37:22 1959
10 Krumbhaar E B and Ehrich W E Varieties of single coronary artery in man occurring as isolated cardiac anomalies Am J M Sc 96:407 1938
11 Nicod J L Anomalie coronarie et mort subit Cardiologia 20 172 1952
12 Hachtel A and Speer F Congen tal absence of right coronary artery Am J Cl Path 21:1035 1951
13 Raekallio J Jr Coexistence of coarct tion of the right pulmonary artery and of the aorta with tricuspid aortic val nd single coronary artery Ann mediat Fenn e 5:320 1959
14 Roberts J F and La be S D Congenital single coronary artery n ma Am Heart J 34 188 1947
15 Sanes S Anomalous orig n and course of the left coronary artery in a ch ld Am Heart J 14 719 1937
16 Senning A Surgical treatment of right entric al outflow stenosis combined with ventricular septal defect nd right left shunt (Fallot s tetralogy) Acta chir scandina 117 73 1959
17 Smith J C Re iew of single coronary with report of t cases Circul tion 1 1168 1950
18 Stapley L A and Ed ards J I Single coronary artery Arch I th 28:217 1939
19 Swan P nd F tzpatrick M Single coronary artery Brit Heart J 16 157 1954
20 Tremouroux J Brasseur I Mcersseman F and La eone I Infarctus myocardique auricu laire et ventriculaire dans un de coronaire unique Acta cardiol 14:574 1959

Experimental and laboratory reports

Participation of the free ventricular walls in the mechanism of production of bundle branch block

Their influence on the morphology of unipolar epicardial tracings

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The presence of conduction disturbances through the branches of the bundle of His raises numerous doubts regarding the manner in which the process of activation takes place in the heart. Much controversy and disagreement is evident in the medical literature in this respect. For some workers the contribution of the vectorial resultant forces of the free walls in the unipolar epicardial morphologies is important. These workers relate the morphology recorded in bundle branch block (BBB) to parietal delays more than to block at the level of the interventricular septum. On the contrary, other workers believe that fundamentally BBB morphologies are caused by the delay of the electrical impulse at the interventricular septum.

Because of this discrepancy, we decided to undertake the present study in order to assess the importance of the depolarization of the free wall of the left ventricle in cases of complete and incomplete left BBB and the depolarization of the free wall of the right ventricle in cases of complete and incomplete right BBB.

Material and method

Forty dogs which ranged in weight between 6 and 10 kilograms were used. Pentobarbital was injected intraperitoneally at the dose of 35 mg. per kilogram. Artificial respiration was given through a tracheal cannula. The heart was exposed through a midline sternotomy. The internal mammary vessels were divided. The pericardium was cut in the midline from the diaphragmatic surface of the heart to its aortic reflection. The phrenic nerve was cut bilaterally. The divided edges of the pericardium were stretched over the lungs and sutured to the cut edges of the sternum.

Throughout the experiments the temperature of the animal was maintained at about 37° C. and blood pressure was continually recorded from the femoral artery. The electrical records were taken with a Schwarzer electroencephalograph Model 504 E with six channels. For the epicardial recordings the electrodes were small steel clamps attached to the epicardium. For the intramural and subendocardial recordings, electrodes which measured less than

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half a millimeter in diameter were mounted at different levels in a lumbar puncture needle and isolated from each other by a dielectric material

The influence of the vectors of the free walls of the ventricles was assessed by a comparative study of the unipolar recordings from the different areas before and after the production of necrosis at different points Necrosis was produced by the injection of chemically pure phenic acid at the sites chosen for each case

The leads employed were Control Lead II (L) unipolar leads to record the different morphologies of the QRS complex at different levels of the free walls of the ventricles and bipolar leads of which the electrodes were separated 0 3 mm from each other These served for the study of the electrical moment of activation and the sequence of the conduction phenomenon of the electrical impulse at the different sites explored

In order to produce BBB the technique of Wilson and associates[7] was used The interventricular septum was tapped with a blunt needle along the path followed by the right or left branches The electrocardiographic paper was run at a speed of 160 mm per second to measure the propagation speed of the impulse However in the figures presented here the paper speed was 60 mm per second Our results were uniform in 85 per cent of the experiments

Results

In the experiment represented in Fig 1 three sites of the free wall of the left ventricle were explored before and after the production of left BBB Point *A* was subendocardial *B* was intramural with the electrode placed approximately at the same distance from *A* and *C* and *C* was subepicardial

Column I of Fig 1 shows control tracing L (upper tracing) which was recorded simultaneously with the subendocardial unipolar tracing obtained at *A* (second tracing) with the intramural unipolar recording obtained at *B* (third tracing) and with the subepicardial unipolar recording obtained at *C* (lower tracing) The unipolar morphologies obtained at *A* and *B* were of the QS type with a negative T wave and a slight degree of S-T segment displacement probably produced by a certain amount of injury caused by the exploring electrode At *C* the complex was of the RS type with a negative T wave In Column II are the morphologies obtained at the same sites after the production of left BBB The first two complexes in Column II show morphologies due to transient complete left BBB then a series of transitional complexes appear which belong to lesser degrees of left BBB which does not entirely disappear because in the last complex of this recording a different morphology from that of the control lead is readily apparent The morphologies of the first two complexes recorded after the production of left BBB (Column II) are of the R or Rs type in points *A* *B* and *C* They are simultaneous in their appearance with respect to each other and with respect to I

As the degree of left BBB decreases these morphologies become less and less similar The morphology of subendocardial and intramural recordings *A* and *B* changed i e a decrease in the voltage of R took place simultaneously with the appearance and gradual increase of the S wave The morphology changed from Rs to RS and finally rS with a simultaneously inscribed intrinsic deflection The subepicardial unipolar recording persisted as an R type of complex and the inscription of its intrinsic deflection took place later than that of recordings from points *A* and *B* As these changes appeared the duration of the ventricular complex decreased and the T wave became less negative because of a diminution of the secondary effect after the diminution of the areas of QRS

Fig 2 belongs to an experiment similar to that represented in Fig 1 Here the free wall of the right ventricle was explored and a right BBB was produced Three more points were explored *A* subendocardial *B* intramural with the electrode placed 2 mm distant from *A* and *C* subepicardial with the electrode placed 2 mm distant from *B*

Column I of Fig 2 shows control tracing L (upper tracing) which was recorded simultaneously with the subendocardial unipolar tracing obtained at *A* (second tracing) with the intramural unipolar tracing obtained at *B* (third tracing) and the subepicardial unipolar recording ob

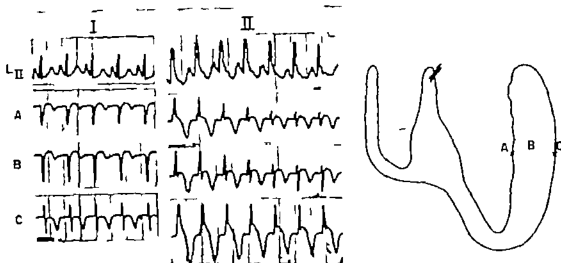


Fig. 1. Unipolar morphologies recorded at three points of the free left ventricular wall (A, B and C) obtained simultaneously with Lead II. Under normal conditions (I) and after the production of left BBB (II). See discussion in text.

tained at C (lower tracing). The morphologies of subendocardial unipolar tracing A and intramural unipolar tracing B were of the rS type, the positive phase of intramural tracing B was slightly larger than that of subendocardial unipolar tracing A. Subepicardial unipolar tracing C had an Rs morphology, and the inscription of its intrinsic deflection took place later than that of subendocardial tracing A and that of intramural tracing B. These facts suggest an activation at these level which runs from A to B and from B to C. In Column II of Fig. 2 are tracings from the same sites after the production of right BBB, the L record (upper tracing) showed a greater duration of QRS and a wide slurred S wave. The morphologies at A, B and C (second, third and fourth tracings in Column II) were of the R type and showed markedly increased slurring. Again the morphologies of tracings from these three points suggest that the free wall of the right ventricle behaves as a volume conductor and that its contribution to the morphologies described above is nil or very poor.

When the degree of block decreased (Column III of Fig. 2), the morphology in the L recording (upper tracing) was of the RS type, but the R was of less voltage and S was deeper than in the control tracing. This indicates that a certain degree of right BBB remained. Despite this, the morphology of the recording made at A became rS in type, at B it became RS in type, and at C it became only positive, i.e., of the R type. This indicates that the activation wave spreads from A to B and from B to C. In other words, again the contribution of the free wall of the right ventricle becomes important in proportion to the decrease in the degree of right BBB.

In order to suppress the influence of the resultant vectors from the free wall of the left ventricle on the morphology of the epicardial recordings, another experiment was carried out, the results of which are shown in Fig. 3. Two subepicardial points were explored: A, the high portions of the lateral wall of the right ventricle, and B, the middle portions of the free wall of the left ventricle.

In Column I, the upper tracing is control record L, the middle tracing shows the unipolar recording obtained at A, and the lower tracing is the unipolar recording obtained at B. These tracings may be considered as control tracings. In Column II are tracings from the same sites after the production of transient left BBB. The complexes are quite characteristic of left BBB, and the morphologies in the L record (upper tracing) and in tracing B (lower tracing) leave no doubt as to the importance of the degree of the left BBB. The

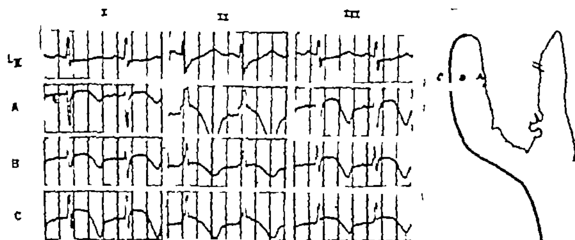


Fig 2 Unipolar morphologies recorded at three points of the free right ventricular wall (A B and C) obtained simultaneously with Lead II Under control conditions (I) with complete transient right BBB (II) and with incomplete right BBB (III)

morphology of the right subepicardial unipolar recording A is of the RS type with a deep slurred and wide S wave

After these tracings were taken time was allowed for the left BBB to disappear so that another control record similar to that in Column I could be made Large and important portions of the free wall of the left ventricle comprising 60 per cent of the free wall of this chamber were then destroyed with phenic acid as shown by the stippled area in the diagram in Fig 3 Tracings taken after this destruction are seen in Column III of Fig 3 The most important change is seen in the tracing taken at B from the necrotic tissue The complex became QS thus indicating the importance of the necrosis Again a left BBB was produced by percussing the bundle of His and the same morphologies were recorded as shown in Column IV of Fig 3 Note that despite the large extent of destroyed tissue the morphologies of the complexes due to left BBB are like those recorded prior to the production of necrosis

The morphology of the left subepicardial unipolar record taken at point B remained predominantly positive of the R type but was of *shorter duration than that of the* control tracing taken at the time of left BBB (lower tracing of Column II Fig 3)

We consider this experiment as quite illustrative of the slight influence of the activation of the free left ventricular wall on the morphologies of complete left BBB

Fig 4 shows another experiment which clarifies some aspects of cardiac activation in the presence of left BBB Three points of the heart were explored A subepicardial on the lateral aspect of the free wall of the left ventricle BB and CC' on the interventricular septum (with close bipolar leads)

Column I shows the unipolar subepicardial tracing obtained at A (upper tracing) and recorded simultaneously with bipolar septal tracings obtained at BB (second tracing) and CC' (lower tracing) The morphology of unipolar subepicardial recording A is of the RS type and the bipolar tracings BB and CC' are simultaneous which indicates an almost simultaneous activation of these points on the septum

Column II presents recordings from the same sites described above after the production of transient left BBB The morphology of the subepicardial unipolar tracing taken at A became predominantly positive of the Rs type with slurring and notching of R and an increased duration of its positive phase The endocardial septal point BB was activated 35 milliseconds *before the intramural septal point* CC' which indicates an important conduction disorder of the left branch The tracing taken with the intramural bipolar lead at point CC' showed an inversion of the greatest deflection indicating a reversal in the sense of the propagation of the impulse

After these tracings were made time was allowed for the left BBB to disappear so that another control record similar to that in Column I might be made

In Column *III* are recordings made with the same leads after the production of transmural necrosis of the free wall of the ventricle at the level of the site explored by the unipolar subepicardial lead *A* as shown in the diagram The morphology of the tracing recorded at *A* was of the QS type as was to be expected in the case of transmural necrosis Tracings recorded with bipolar leads at *BB* and *CC* continued to be simultaneous and indicated no disturbance in the conduction of the left branch A complete transient left BBB was produced later and the tracings are shown in Column IV The first two complexes obtained in *A* were identical with those in Column II Under these circumstances point *CC* was activated 35 milliseconds after the activation of point *BB* thus demonstrating the same degree of left BBB as was seen in control Column *II* In regard to the last two complexes of Column IV a decrease in the time of activation between points *BB* and *CC'* takes place Indeed septal point *CC* is activated 15 milliseconds after septal point *BB* and the greatest deflection in the tracing from that point again becomes positive indicating that the degree of left BBB decreases significantly The morphology of the unipolar subepicardial tracing from *A* changed from Rs to rS Since the electrode exploring point *A* recorded the variations in intracavitary potential once the vectorial forces of the free wall of the left ventricle had been eliminated by means of necrosis it was to be expected that the changes taking place in the positive deflection of the recording obtained at *A* originated in the variations in potential of the interventricu

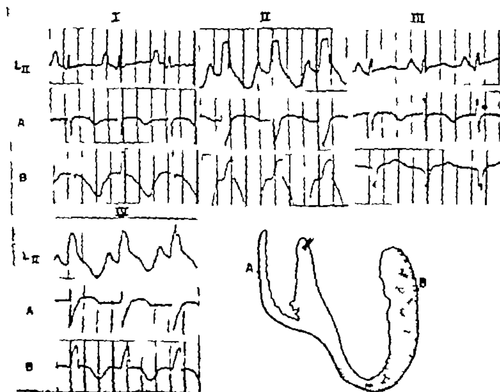


Fig 3 Lead *II* with simultaneous recordings from two epicardial points one in the free wall of the right ventricle (*A*) and the other in the free wall of the left ventricle (*B*) Under control conditions (*I*) after the production of transient left BBB (*II*) with necrosis of the free wall of the left ventricle as shown in the diagram and without conduction disturbances of the left bundle branch (*III*) with parietal necrosis and complete left BBB (*IV*)

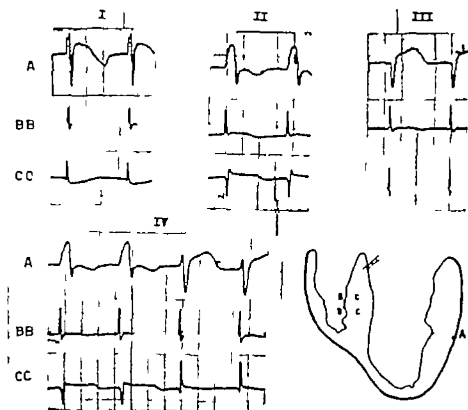


Fig. 7 Unipolar epicardial lead record obtained from the free wall of the left ventricle (*A*) simultaneously with proximal bipolar lead tracings from the right endocardial surface (*BB*) and from the thickness of the septal mass (*CC*). Under control conditions (*I*) with transient complete left BBB (*II*) with transmural necrosis of the free wall of the left ventricle and without conduction disturbances of the branch (*III*) with transmural necrosis of the free wall of the left ventricle and with complete block of the left bundle branch (*IV*)

lar septum which is a direct function of the degree of block

Fig 5 illustrates the findings in an experiment in which two points of the free wall of the right ventricle were explored with unipolar leads *A* corresponds to the unipolar lead exploring the subendocardial surface at the trabecular zone and *B* to the unipolar lead at the subepicardial surface on the same lead line as unipolar subendocardial lead *A*

Control Column I shows the L record (upper tracing) which was recorded simultaneously with the tracings of subendocardial unipolar lead *A* (second tracing) and subepicardial unipolar lead *B* (lower tracing) It is apparent that unipolar subendocardial tracing *A* shows an rS morphology whereas in tracing *B* the rS morphology persists although R is of greater voltage than that seen in *A* This fact indicates that the greater voltage of R in the unipolar tracing *B* is given by the activation of the muscular mass between *A* and *B* Column II shows recordings made in the same previously described leads after the production of transient complete right BBB Under these circumstances L became type RS with notchings and slurrings of the S wave and a greater duration of QRS than under control conditions as seen in Column I These changes show the importance of the conduction disorder of the right bundle branch The tracings obtained with unipolar subendocardial lead *A* (second tracing) and unipolar subepicardial lead *B* (lower tracing) show predominantly positive morphologies of the R type with a duration of the QRS greater than that of the control recording The initial parts of these two morphologies are simultaneous

Once the right BBB had disappeared and the electrocardiographic recording returned to control conditions as in Column I a transmural necrosis of the free wall of the right ventricle was produced at the sites explored *A* and *B* as shown in the diagram The results are shown in Column III where it may be seen that the unipolar recordings from points *A* and *B* became similar i e the high R wave in the tracing made at point *B* disappears This fact shows that the R wave recorded by the subepicardial lead *B* was due to the activation of the underlying muscular mass at point *B*

The tracings of Column IV were recorded after the production of transmural necrosis of the free right ventricular wall and complete right BBB The morphologies of the L~II~ record (upper tracing) are similar to those in Column II a fact which indicates that there is a certain degree of right BBB similar to that registered as a control or a reference in the same Column II The unipolar subendocardial recording *A* and subepicardial *B* show predominantly positive morphologies of the R type with duration of QRS greater than that seen in Columns I and III and with a simultaneous initial deflection It may also be seen that the morphologies of the unipolar recordings obtained at *A* and *B* under these circumstances are very similar to those of control tracings in Column II

The experiment illustrated in Fig 6 was similar to the one described in Fig 5 except that this time the free wall of the left ventricle was explored Two points of the middle portion of the lateral aspect of the wall were explored with unipolar leads *A* subendocardial and *B* subepicardial at the same level as *A*

Column I shows the L record (upper tracing) which was recorded simultaneously

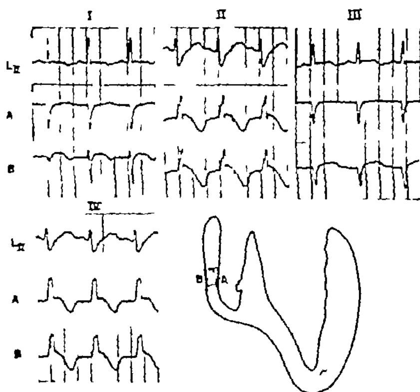


Fig 5 Lead II recorded simultaneously with unipolar morphologies from two points in the free wall of the right ventricle *A* subendocardium and *B* subepicardium at the same level as *A* L under control conditions (*I*) with complete transient right BPB (*II*) with transmural necrosis as shown in the diagram and without conduction disturbance of the branches (*III*) with transmural necrosis and complete right BBB (*IV*)

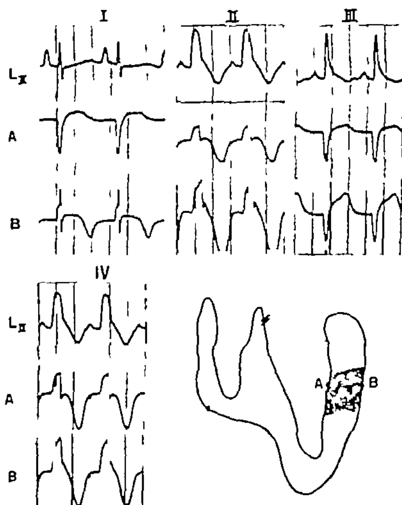


Fig 6 Lead II recorded simultaneously with tracings from two points in the free wall of the left ventricle *A* subendocardium and *B* subepicardium Under control conditions (*I*) with complete transient left BBB (*II*) with transmural necrosis of the free wall of the left ventricle and without conduction disturbances of the branch (*III*) with transmural necrosis and left BBB (*IV*)

with the unipolar subendocardial tracing obtained at *A* (second tracing) and the unipolar subepicardial tracing obtained at *B* (lower tracing) The former shows QS complexes and the latter shows RS complexes These are control tracings

Column II shows tracings recorded with the same leads after the production of transient complete left BBB The L_{II} record became predominantly positive with a duration of QRS greater than that seen in control Column I and with notching and slurring of R a fact which denotes the importance of the degree of left BBB The tracings obtained with unipolar subendocardial lead *A* and subepicardial lead *B* became predominantly positive of the R type with a duration of QRS greater than that seen in control Column I These morphologies (L_{II} *A* and *B*) may be taken as control or reference tracings for left BBB

After the transient left BBB had disappeared and the electrocardiographic tracings had returned to the control conditions of Column I a transmural necrosis of the free wall of the left ventricle was produced as shown in the figure This necrosis involved the muscular mass explored by the electrodes at points *A* and *B* Column III shows the tracings recorded Subendocardial unipolar morphologies (second tracing) were still of the QS type like those of

control Column I The unipolar subepicardial morphologies were also of the QS type and this would seem to be due to the destruction of the muscular masses responsible for the vectorial forces which gave the R wave of the subepicardial recording

The tracings of Column IV were recorded after transmural necrosis of the free left ventricular wall and complete left BBB had been produced The L record (upper tracing) shows the same features described in the control tracing of Column II The unipolar subendocardial recording *A* and the subepicardial unipolar recording *B* show morphologies with characteristics very similar to those obtained in the control tracings of Column II (second and third tracings) that is they became predominantly positive with duration of QRS greater than in the control lead with notchings and slurrings of R

Discussion

The use of a method which eliminates muscular areas of the ventricular walls with consequent elimination of the vectorial forces of these areas permitted us to study the influence of these vectorial forces on the unipolar morphologies recorded at different levels of the free wall of the ventricles and with different degrees of BBB

That the vectorial forces of the free wall of the ventricles present in the control tracings had been eliminated became evident in the disappearance of the epicardial deflection after the production of necrosis of the explored areas

Our experiments show that when there is a complete BBB the morphologies of the unipolar recordings obtained in the entire thickness of the free wall on the same side as that in which the block exists are produced fundamentally by potentials originated at the level of the interventricular septum a fact which was proved initially by Medrano and associates[4] and later by Anselmi and associates [5] In fact the simultaneously inscribed records of the points explored in the subendocardial intramural and subepicardial portions of the free wall of the blocked side speak in favor of the view that the vectorial forces which give rise to these morphologies originate at points other than in the free wall of the ventricle This is proved by the persistence of the morphologies of the unipolar recordings after elimination by means of the parietal necrosis of the vectorial forces originating in the free wall of the ventricle The free walls of the ventricles behave as conductors in the presence of complete BBB and the vectors originated through their activation have slight influence on the morphologies of the unipolar recordings obtained at different levels

Our experiments afford evidence contrary to the view held by those who attribute the unipolar morphologies of BBB to delays of the impulse at the level of the free walls of the ventricles In fact if the impulse suffered any delay in the speed of propagation at the level of the muscular mass of the free walls of the ventricles one should expect an alteration in their morphology once the muscular mass was destroyed But this was not seen in any of our experiments Likewise we cannot admit the explanation proposed by some workers according to whom the activation of the free wall in the case of BBB progresses from the apex to the base of the heart with a front wave which is perpendicular to the endocardial and epicardial surfaces If this were true once the wave of activation passed the explored points of the free wall to ascend to the basal portions it would produce an important negative wave at those points giving rise to RS complexes instead of R or Rs morphologies as were obtained in our experiments On the other hand if these morphologies had their origin in the same free walls a modification in the recordings should be expected once the muscular masses giving rise to them had been destroyed Again this was never seen in our experiments

By application of the concept of electrical window [4] the variations in potential recorded at the epicardium of a necrosed portion should be attributed to the variations in potential of the ventricular cavity toward which the exploring electrode is oriented For this reason the progressive decrease in the positive deflection which takes place in the unipolar recording obtained at the epicardium of the necrosed area as the block decreases must be attributed to a decrease in the vectorial forces

originated at the interventricular septum The variations of the septal potential are directly proportional to the degree of BBB As the septal vectorial forces decrease as a result of a lesser degree of BBB their influence on the epicardial unipolar recording becomes shorter and less important Under these circumstances the vectors which result from the activation of the free wall of the ventricles manifest themselves adding their action to the septal resultants This causes the unipolar epicardial recordings to be influenced by these two vectorial forces septal and free wall The unipolar morphology obtained at the epicardium of the side homologous to the block does not show significant changes when the block is complete or when this block decreases In the first case the morphologies are primarily conditioned by differences in septal potential whereas in the case of a lesser block both factors contribute (1) the septal vectorial resultants whose influence is directly related to the degree of block and (2) the vectorial forces originating in the free wall of the ventricle of later appearance than those of the interventricular septum

From a practical standpoint it is difficult to determine when a given morphology corresponds to a complete block and when to an incomplete block since at the present time the information supplied by the electrocardiogram makes it impossible to assess the participation of each component

Summary

A study has been made of the influence of the vectorial resultants of the interventricular septum and those of the free walls of the ventricles on the unipolar recordings at different levels of the free wall of the ventricles with different degrees of bundle branch block (BBB)

The influence of the vectorial resultants of the free walls of the ventricles was assessed by a comparative study of the unipolar morphologies recorded at different points of the wall before and after the production of parietal necrosis at the same point the lead

The importance of the vectorial forces of the interventricular septum on the unipolar morphologies of BBB becomes apparent when the block is complete Our evidence indicates that the vectorial forces of the ventricular septum are directly related to the degree of block and that when the resultant vectorial forces of the ventricular septum decrease because of a diminution in the degree of BBB the vectorial forces of the free wall of the ventricle on the side homologous to the block become manifest

REFERENCES

1 Bryant J M Interventricular conduction *In* Kossmann C E editor Advances in electrocardiography New York 1958 Grune & Stratton Inc
2 Alzamora Castro V Battilana G Abugattas R Rubio C Bouroncle J Zapata C and Santa Maria E Los bloqueos intraventriculares (estudio electrocardiografico) An Fac Med Lima Peru 34 313 1951
3 Erickson R V Scher A M and Becker R A Ventricular excitation experimental bundle branch block Circulation Res 5 5 1957
4 Rodriguez M I and Sodi Pallares D The mechanism of complete and incomplete bundle branch block Am Heart J 44 715 1952
5 Medrano G A Sodi Pallares D Marasco F and Bisteni A The importance of septal activation in the electrogenesis of the unipolar morphologies bundle branch block experimental study with total extirpation of the free ventricular wall of the blocked ventricle Am Heart J 126 1959
6 Anselmi A Gonzalez J Alvarez M Garrido T and Chacon V Significado electrofisiologico de las deflexiones ventriculares 1 Contribucion de las paredes libres ventriculares en distintas modalidades de activacion ventricular Arch Inst cardiol Mexico 30 286 1960
7 Wilson F N and Herrmann G R An experimental study of incomplete bundle branch block and of the refractory period of the heart of the dog Heart 8 229 1921
8 Wilson F N Johnston F D Rosenbaum F F Erlanger H Kossmann C E Hecht H H Cotrim N Menezes de Oliveira R Scarsi R and Barker P S The precordial electrocardiogram Am Heart J 27 19 1944
9 Burchell H B Essex H E and Pruitt R D Studies on the spread of excitation through the ventricular myocardium II The ventricular septum Circulation 6 161 1952

Clinical estimation of the volumes of blood in the right heart, left heart, and lungs by use of I^{131} albumin

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After I^{131}-labeled human serum albumin has been injected intravenously, the radioactivity of an organ parallels its plasma content until a significant amount of the I^{131} has escaped from the vascular compartment. If the total radioactivity of an organ or region could be measured accurately in vivo, its plasma content could be determined by comparing the radioactivity per unit volume of plasma with the activity of the whole organ. In the case of the heart, most of the observed radioactivity would be derived from plasma within the cardiac chambers rather than the coronary vessels. By application of the principles developed for the analysis of the dilution of dye in flowing blood,[1] it would be possible to estimate the volumes of blood in the right heart and the left heart and in the lungs. The present study was done to test the principles and define some of the problems of such measurements.

Materials and methods

Subject. Fifteen hospitalized subjects with no evidence of heart disease were compared with 26 patients under treatment for cardiovascular disease. The diagnoses in the latter group were: essential hypertension, 8; arteriosclerotic heart disease, 2; myocarditis of unknown etiology, 2; massive pericardial effusion due to carcinoma and to lupus erythematosus, 1 each; thyrotoxic heart disease, 1; syphilitic heart disease, 1; rheumatic heart disease involving mitral and aortic valves, 2; rheumatic aortic stenosis with insufficiency, 2; and rheumatic mitral stenosis, 6.

Placement of the counter. Each subject was fluoroscoped in the supine position and the surface projections of four locations were indicated on the anterior chest wall. These were the cardiophrenic angles and two points on the opposite borders of the cardiac shadow immediately below the pulmonary artery. A four-sided cardboard pattern was constructed with dimensions based on these points. This was used to guide in the placement of lead shielding so that the center of the crystal, the inner edge of the shielding placed over the chest wall, and the border of the cardiac shadow would fall along a straight line. With this arrangement all of the scintillation crystal could be seen from any point within the heart and at the same time as much tissue to either side of the heart as possible

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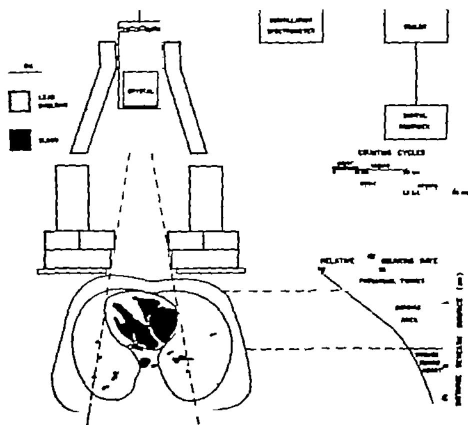


Fig 1 The arrangement of apparatus for determining radioactivity of the cardiac region after intravenous injection of I^{131} albumin The relative counting rate of an I^{131} source at varying depths in a masonite phantom is shown

was eliminated (Fig 1) The heavily shielded 2 inch by 2 inch cylindrical NaI crystal was positioned over the center of the heart 25 cm from the anterior chest wall The scintillation pulses corresponding to energies below 0 15 Mev were eliminated by a spectrometer and the remainder were recorded automatically every 0 3 to 0 5 second by a Hewlett Packard 560 A digital recorder

Injection of I^{131} albumin One hundred microcuries of radioiodinated human serum albumin (Albumotope Squibb) was injected into a medial antecubital vein and was followed by a flush of 5 10 ml of 0 8 per cent NaCl solution The injection time ranged from one to several seconds The activity of the I^{131} albumin solution was determined in a weighed dilution employing a 1 per cent aqueous detergent solution (Alconox)[3] and assayed with Geiger Muller tubes[4] The quantity injected was equal to the amount placed in the syringe determined gravimetrically less that which could be recovered in washings from the syringe and needle after the injection In 9 lots of labeled albumin 3 0 ± 0 9 per cent of the radioactivity was not precipitated by addition of saturated ammonium sulfate and centrifugation at 20 000 RCF No correction for this apparently unbound activity was made[5]

Measurements after isotope injection Radioactivity of the cardiac area was recorded for 10 minutes Blood was then collected from a second vein into a tube containing dry heparin and the hematocrit was determined by centrifugation for 45 minutes at 2 000 RCF correcting for 3 per cent trapped plasma

Calculations

Plasma volume The observed dilution of the total amount of labeled albumin was used for calculating total plasma volume assuming that complete mixing and no loss of tracer from the blood had occurred 10 minutes after the injection

Blood volume The total blood volume was estimated from the plasma volume and the venous hematocrit No allowance was made for a lower total body hematocrit

Total intracardiac blood volume By comparison of the activity over the precordium 10 minutes after injection of the isotope with that of the peripheral venous blood at the same time the total intracardiac blood volume was estimated An I^{131} albumin source of known strength was counted under the conditions employed for the subjects at increasing depths within a phantom of masonite a fiberboard with density approximating that of tissue (Fig 1) The mean counting rate of 1 microcurie of I^{131} within the zone occupied by the average normal heart was calculated and related to the counting rate per microcurie of I^{131} observed with the Geiger Muller tube employed in all studies With the particular instruments and techniques employed 1 μc of I^{131} produced 265 000 cpm with Geiger Muller counting and 1 600 cpm when evenly distributed along the anterior posterior axis of the cardiac area Therefore for these particular counters intracardiac blood volume in milliliters was estimated from

$$\frac{\text{Precordial radioactivity (cpm)}}{\text{Whole blood radioactivity (cpm/ml)}} \times 166 \qquad (1)$$

Both counters were standardized with known sources before each use but no corrections for changes in counter sensitivity were made since only minor variations occurred

Right and left sided components of the intracardiac blood volume A semilogarithmic plot was made from the digital record of radioactivity of the cardiac region (Fig 2) In all but 4 instances these graphs demonstrated 2 peaks during the first circulation of the isotope through the heart and lungs corresponding approximately to the periods of maximal concentration of isotope in the right and left sides of the heart Curves *a* *b* and *c* in Fig 2 are representative of measurements in 23 subjects in whom it was believed possible to make a meaningful linear extrapolation of the decline of radioactivity in the right heart The lowest concentration observed between the peaks in these subjects averaged 0 51 ± 0 10 times the peak concentration in the right heart In Fig 2 curve *a* is a typical result *b* is one in which the right sided component is unusually well defined and *c* is of borderline quality for extrapolation The left sided component was obtained by subtraction and similarly extrapolated on the assumption that this decline also was linear with time Curve *d* was obtained from a subject with a large heart and low cardiac output It is clearly unsatisfactory for attempting such a division There were 10 such instances In the study represented by curve *e* of Fig 2 there was a bifid right ventricular component presumably caused by irregular outflow of the isotope from the arm There were 5 such curves In 2 subjects the apparent slope of the left sided curve was steeper than the right (Fig 2 *f*) This was thought to represent inaccurate extrapolation of the right component or a changing rate of blood flow In one subject the injection was incomplete In these studies no calculations based on separation of the two sides were made

The portion of the total intracardiac blood volume contained in each side of the heart was estimated from the relative areas of the right and left components of the curves *of precordial radioactivity* The rationale of this calculation was as follows The precordial radioactivity at any time during the first passage of the isotope was assumed to be proportional to the total amount of isotope within the combined right and left sides of the heart at that instant Since the mean volumes of the two sides do not change significantly during this period the height of the right and left components of the curve were proportional not only to the total amount but also to the average concentration of isotope within each of these segments at any instant throughout the period of the first passage of the isotope However since the amount of blood on the two sides is not equal the heights of the two curves do not indicate the relative concentrations per milliliter of blood on the two sides In each cardiac chamber

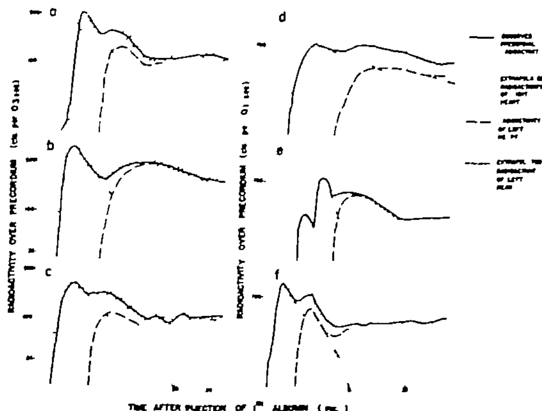


Fig. 2. Precordial radioactivity after the intravenous injection of I^{131} albumin in 6 subjects. Radioactivity is shown on a logarithmic scale. Curves a, b, and c were satisfactorily divided into right and left heart components, whereas in d, e, and f this was not possible.

$$I = F \times T \times A \tag{2}$$

where I is the quantity of isotope passing during the first circulation, F is the volume of blood flow per unit time, T is the time required for the initial passage of the bolus of tagged blood, and A is the average concentration of tracer in the blood during the initial passage. But

$$A = \frac{Ac}{T} \times K$$

where Ac is area under the concentration-time course curve during the first circulation and K is a proportionality constant. Therefore

$$I = F \times Ac \times K$$

or

$$Ac = \frac{I}{KF}$$

Since $\frac{I}{KF}$ in the right and left sides of the heart is equal, Ac is also equal in the two sides.

When the monitor is recording equally from equal volumes of blood in the right and left sides of a heart without a shunt, the areas of the right and left precordial curves are necessarily equal. The actual observed areas of these curves must be proportional to the volumes of blood effectively monitored. The remote placement of the crystal and the arrangement of precordial shielding so that all of the heart would be seen by the monitor was intended to provide equal geometric representation of all blood within the heart.

Pulmonary blood volume. The mean circulation time from right heart to left heart was calculated arithmetically from the concentrations at one-half second intervals[3] in those measurements in which right and left components were separated. The volume of blood between the right and left sides is defined by this mean circulation time and the cardiac output. It is clear that this volume as measured in these subjects includes a portion of the intracardiac volume. As an aid in finding a

useful correction for this intracardiac contribution, a simple model was used which is outlined in Fig. 3. Results obtained with this model are given in Table I. When one half of the intracardiac volume was subtracted from the total, an accurate result for pulmonary volume was obtained. This correction was also applied to the data from man.

Cardiac output. Cardiac output (F) was calculated by the method of Huff and associates[7] and Veall and associates,[ ] making use of the average concentration within the right and left hearts combined during the first passage of isotope (A), the time required for the first passage (T), the concentration in the blood after complete mixing of the isotope at 10 minutes (C), and the blood volume (BV).

$$F = \frac{(C) \times (BV)}{(A) \times (T)} \qquad (3)$$

Results and interpretation

Intracardiac blood volume. Intracardiac blood volume ranged from 370 to 2,100 ml., averaging 345 ± 55 ml./M.² or 614 ml. total, in 16 subjects without evidence of heart disease. The relation of these estimates to the approximate size of the precordial projection of the heart is shown in Fig. 4. In both of the subjects with known pericardial effusion, there was approximately 500 ml. less intracardiac blood than would have been expected from the size of the heart shadow. This large variation from the mean relationship is probably caused by the effusion which enlarges the cardiac shadow and partially shields the intracardiac blood from the counter. In the group of 21 determinations in which the size of the heart shadow of those with and without heart disease overlapped, there was less intracardiac blood for a given size of heart shadow in those with heart disease ($p = 0.04$). The presence of ventricular hypertrophy in the latter group seems to be the most obvious explanation for this difference which is shown more clearly in Fig. 5. The 11 subjects with heart disease suffered from hypertension or rheumatic valvular deformity. Myocardial hypertrophy was prominent clinically in this group, but dilatation was minimal.

Blood content of the right and left sides of the heart. The partition of intracardiac volume was estimated in 23 subjects. In those without heart disease the volume of the right heart averaged 170 ± 25 ml./M.² and that of the left heart 185 ± 50 ml./M.² The average body surface area of this group was 1.82 M.² Fig. 6 shows the division of the intracardiac blood. This did not correlate well with the side of the predominant ventricular dilatation as judged from clinical data. Atrial blood is included in the volume measured, and bilateral enlargement of the heart was present in many instances.

Pulmonary blood volume. In 9 subjects without heart disease, pulmonary blood volume was 490 ± 130 ml./M.² or 16.5 ±

*Table I. Results of all determinations of the volume of the pulmonary component of a vascular model**

Number	Rate of flow (ml./min.)	Mean circulation time (right to left) (sec.)	Calculated pulmonary volume (ml.)	Sum of actual pulmonary volume and one half of chamber volume (ml.)	Actual pulmonary volume (ml.)	Combined chamber volume (ml.)
1	461	16.2	124.5	123.0	65.1	115.7
2a	218	33.6	122.1	123.0	65.1	115.7
3a	343	21.7	124.1	123.0	65.1	115.7
1b	279	20.5	95.3	96.3	38.4	115.7
2b	203	30.6	106.1	96.3	38.4	115.7
3b	244	3[illegible].8	96.8	96.3	38.4	115.7

*[illegible] principles [illegible] applied to the analysis of [illegible] and monitoring of the flow of bolus of radioactive material through the model. Rate of flow and pulmonary volume were varied. Calculated pulmonary volume closely approximated the sum of the actual pulmonary volume and one half of the chamber volume.

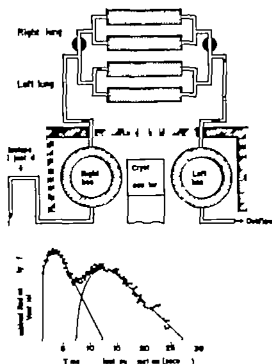


Fig 3 Model demonstrating pulmonary blood volume determination The chambers are partly filled with glass beads to insure mixing of isotope and water The scintillation counter is shielded from radiation originating in the lungs One curve obtained is illustrated

3 7 per cent of the total blood volume The results were essentially the same in patients with heart disease including those with mitral stenosis (Fig 7) The degree of variation was marked

Discussion

Measurement of intracardiac volume The inability to obtain adequate depth focus with scintillation detectors presently in use is a major limitation in most isotope techniques making use of in vivo monitoring The anterior chest wall the myocardium the pulmonary vessels adjacent to the heart, and the structures of the posterior mediastinum spine and posterior chest wall all contain blood that is within the field of the counter as employed in these studies The combined effective volume of these tissues is probably small compared to the intracardiac volume partly because of the absorption of radiation from the deeper structures This decrease in effective counting rates at increasing depths is one of the sources of error which makes the use of a single calibration factor for all hearts necessarily erroneous The marked differences observed in the 2 subjects with pericardial effusion are encouraging and suggest a diagnostic application of this technique The method in its present form appears to be sensitive to the presence of myocardial hypertrophy This suggests that the variations in extracardiac contributions to the measured volume and in the factors affecting the true calibration for external counting may not be so great as might be supposed The major error in the division of the total volume between right and left sides probably arises in the extrapolation of the observed data The somewhat more posterior position of the left ventricle and the added shielding from its thicker wall may lower the counting rate from the blood within the left side of the heart somewhat Sutton and co workers[9] have shown that red cells injected into the pulmonary artery of man begin to appear in the right ventricle in 7 to 9 seconds Therefore significant recirculation of isotope into the right heart probably occurs early on the downslope of the curve of the left side of the heart This may be a significant source of error in the extrapolation of this component

Prinzmetal and co workers[10] suggested the use of radiocardiography to distinguish myocardial hypertrophy from chamber dilatation, and Shipley and his associates[11] noted that the area under the right or left component was correlated with the volume of the chambers They believed that the detection of enlargement of the combined atrial and ventricular chambers might be possible although no such study was reported Similar suggestions have been made by Huff and associates[12]

The intracardiac blood volume can be estimated from the difference between the total heart volume as calculated radiologically from the heart shadow in vivo and the volume of the cardiac muscle at post mortem examination From radiographic studies Liljestrand and associates[13] have obtained mean values for the total volume of the living heart ranging from 700 to 750 ml Since the volume of the normal heart muscle as estimated from its weight is approximately 260 ml the normal total intracardiac blood volume as judged by this method is in the range of 440 to

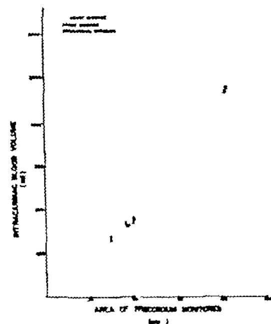


Fig 4 Relation of intracardiac blood volume in 41 subjects with and without heart disease to the size of the heart shadow The heart size is indicated by the area of precordium monitored during the determination of cardiac radioactivity

490 ml The average in the present isotope study was 614 ml total volume Another approach is to measure the amount of liquid required to fill the cardiac chambers at autopsy Velazquez[19] obtained total volumes of from 108 to 298 ml in 12 normal hearts filled with a paraffin mixture Soloff and Zatuchni have introduced a method of calculating the volumes of the four chambers by means of simultaneous biplane stereoscopic angiocardiograms They studied 18 patients with mitral stenosis and found an average 887 ml (range 595 1 341 ml) for the total capacity The average volume in 6 subjects with mitral stenosis in the present group was 692 ml The fractional discharge rate of dye or I^{131} albumin from the intracardiac cavities has been used as the basis for estimates of ventricular volume [21] but the errors inherent in these methods have not as yet been adequately defined

Pulmonary blood volume The errors which affect the separation of the right and left curves for the partitioning of intracardiac volume are also involved in the calculation of the mean pulmonary circulation time upon which estimation of the pulmonary blood volume depends The basic validity of the dye dilution method for the determination of cardiac output has been extensively discussed in the recent literature and the related techniques employing injection of isotopes and external monitoring have been well described The particular method of estimating cardiac output used in the present study does not differ greatly from those employed by others in work which has demonstrated the accuracy of this approach Technical problems have been considered in detail by MacIntyre Pritchard and Moir [12] These authors have suggested that the absence of an increase in precordial radioactivity after the first circulation was one indication that the equilibrium observation was made on the same volume of blood monitored during the initial circulation In the present group of determinations the precordial radioactivity immediately after the left ventricular downslope averaged 1 12 ± 0 14 times the concentration at 10 minutes It is possible that the particular correction for the volume of blood within the heart in the present technique may have a sound theoretical basis provided that adequate mixing and equal geometric representation of the two sides of the heart to the counter are achieved It has been repeatedly pointed out that only actively circulating blood is measured by the dye

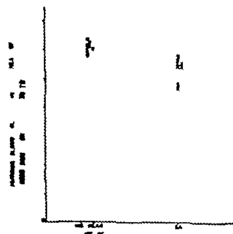


Fig 5 Comparison of the ratio of intracardiac blood volume to the area of the heart shadow in group of subjects with normal hearts and in a group with heart disease The sizes of the heart shadow are in the same range for the two groups

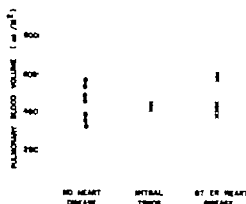


Fig 6 Division of intracardiac blood volume between the right and left sides of the heart in subjects with normal hearts and in those with ventricular enlargement

dilution approach This may be one of the factors responsible for the large variation in results which has been found in this and other studies[11] No correction for the low hematocrit of small pulmonary vessels has been applied since this is probably a small error[20 1]

Many variations of the dye dilution approach have been applied to the estimation of pulmonary or central blood volume A number of groups have made simultaneous determinations of cardiac output and the time required for substance injected into a vein or the right heart to reach a peripheral arterial site usually the brachial or femoral artery An early study employing the fastest rather than the mean circulation time was made by Stewart[22] Ebert and his associates[23] found that the volume measured by injection into the pulmonary artery and sampling from a femoral artery averaged 605 ml /M[2] of body surface and Doyle and co workers[24] obtained an average result of 634 ml /M when arterial samples were collected from a radial artery Hetzel and others[25] obtained a mean result of 1 081 ml /M[2] with sampling from the radial artery for a similar procedure Kopelman and Lee[26] reported a mean volume of 1 140 ml /M[2] between antecubital vein and brachial artery and 770 ml /M[2] when the injection was given in the main pulmonary artery Braun and associates[27] found mean total volumes of from 910 to 1 120 ml measured from antecubital vein to brachial artery corresponding to approximately 600 ml /M[2] It has recently been demonstrated[11 28] that local hyperemia or vasoconstriction of the extremity from which samples are taken has a marked effect on the arterial concentration curve and on central volume determined by this method In an early study Blumgart[29] estimated the true pulmonary blood volume to be of the order of 589 ml total Lagerlof and associates[31] injected dye into the pulmonary artery and made corrections for the blood within the arteries and left side of the heart Values averaging 595 ml /M[2] were obtained Kraus and associates[32] injected dye into the pulmonary artery and I[131] albumin into the left atrium simultaneously and sampled from the brachial artery The average pulmonary volume in patients with normal dynamics was 260 ml /M[2] which is considerably lower than estimates made by any other technique A similar study by McGaff and associates[33] resulted in a mean figure of 370 ± 40 ml /M[2] in 13 subjects with rheumatic heart disease

Shipley and co workers have pointed out the feasibility of calculating from the radiocardiogram the mean circulation time from right heart to left heart They have reported an average value of 6 5 seconds in normal subjects but no simultaneous measurements of cardiac output were made Several methods of estimating pulmonary circulation times have also been described by Gigli and associates[34] Lammerant and DeVisscher[35] have reported determinations of the mean pulmonary circulation time and the circulating pulmonary blood vol



Fig 7 Pulmonary blood volume in patients without cardiac disease in those with mitral stenosis and in those with other types of heart disease

ume in man by means of I^{131} albumin and precordial monitoring as has been done in the present study. The mean circulating pulmonary plasma volume in 57 normal subjects was 326 ml./M.² ranging from 195 to 640 ml./M.² This corresponds to a blood volume of approximately 550 ml./M.² These results closely approximate those of the present series. A study by Eich and co-workers using somewhat different techniques resulted in a mean estimate of pulmonary blood volume of 436 ml./M.² and another study by Moir and Gott resulted in a figure of 610 ml./M.² The latter authors question the applicability of such techniques to the study of pulmonary blood volume because of the probable failure of an unpredictable portion of pulmonary blood volume to participate in the primary dilution curve. The essential agreement of the Stewart-Hamilton technique with the equilibration technique of Bradley as tested by Rabinowitz and Rapaport[17] in dogs is evidence tending to make this possibility less likely, since the time allowed for mixing is increased several fold in the equilibration technique. Attempts at a more direct type of determination based on isotope dilution in blood before and after release of an occlusion of the circulation to one lung have not been convincing. Still another approach is based on the analysis of the slope of indicator curves recorded from a peripheral artery after injection into the right heart.[18] Reasonable figures have been obtained in man,[19] but in comparison with several techniques in dogs[1] the results with this technique were 25 per cent lower than those with the Stewart-Hamilton or Bradley techniques. Hetzel and associates[20] have noted an increase in apparent pulmonary volume when the injection is given at increasing distances proximal to the lung. This finding indicates that the assumptions on which the calculation of pulmonary blood volume by the slope method is based may not apply.

Summary

1. An external isotope method for estimating intracardiac and pulmonary blood volumes has been studied in 41 subjects with and without cardiac disease.

2. Intracardiac blood volume estimated from radioactivity of the cardiac area 10 minutes after intravenous injection of 100 μc of I^{131} albumin averaged 345 ± 55 ml./M.² in 16 subjects without heart disease.

3. In general, intracardiac blood volume was proportional to the size of the heart shadow, but there was slightly less blood in relation to the size of the heart in subjects with cardiac hypertrophy. In 2 persons with pericardial effusion the intracardiac blood volumes were approximately 500 ml. less than would have been expected from the size of the cardiac shadow, suggesting an area of diagnostic usefulness for this technique.

4. By dividing the curve of precordial radioactivity during the first circulation of the isotope into the right and left heart components, the portion of the intracardiac blood in each side of the heart and the pulmonary blood volume were estimated.

5. The right heart volume in subjects without heart disease was 170 ± 25 ml./M.² and the left heart volume was 185 ± 50 ml./M.²

6. In normal subjects pulmonary blood volume was 490 ± 130 ml./M.² Similar results were obtained in subjects with mitral stenosis and with other forms of heart disease.

7. The isotope methods used in the present studies contain important technical defects. Accurate and reliable techniques will require further development of instrumentation and procedure.

References

1. Stewart, G. N.: Researches on the circulation time in organs and on the influences which affect it. J. Physiol. 15:31, 1894.
2. Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G.: Studies on the circulation. IV. Further analysis of the injection method and of changes in hemodynamics under physiological and pathological conditions. Am. J. Physiol. 99:534, 1932.
3. Sear, H., Allen, T. H., and Gregersen, M. I.: Simultaneous measurement in dogs of plasma volume with I¹³¹ human albumin and T-1824 with comparisons of their long term disappearance from the plasma. Am. J. Physiol. 240, 1953.
4. Burch, G., Reaser, P., Ray, T., and Threefoot, S.: A method of preparing biologic fluids for counting of radio elements. J. Lab. & Clin. Med. 35:626, 1950.
5. Franks, J. J., and Zizza, F.: Simultaneous measurement of plasma volume in man with T-1824 and an improved I¹³¹ albumin method. J. Appl. Physiol. 13:299, 1958.

6 Huff R L Feller D D
Cardiac output by body surf
I[131] human serum albumin
33:944 1954
Huff R L Feller D D Jud
Bogardus, C M Cardiac outp
dogs measured by m
(I) human serum albumin
1 564 1955

8 Veall N Pearson J D
Lowe A L A method for
of cardiac output (prelimin
ceedings of Second
Oxford 1954 Lond 19
Scientific Publications p 18
et al

9 Sutton C C
Studies on the
circulation in man
1950

10 Prinzmetal M Cord
and Flieg W
clinical applications, J A M A 1 9

11 Shipley R A Clark R
and Krohmer J
cardiogram in heart failure
1953

1 Huff R L Parrish D
A study of circulation
crystal radiation detectors
thoracic wall Circulation

13 Liljestrand G
Zachrisson C C The
in man Am HEART J 1 406 19

14 Smith H L The weight of the
HEART J 4 9 19

15 Velasquez T Capacity
cardiaca en estado normal
Int card M 20:495 1950

16 Sokolow L
volumes and their
heart disease
Circulation 19:269 1950

1 Bing R J Heimbecker R and Falholt W
An estimation of the residual volume of
in the right ventricle of normal and
human heart Am HEART J 42 1
1951

1 Falholt W Mathematical
siderations concerning the residual volume of
the heart ventricles, Scand J Clin
Invest 8 6 1956

19 Gale C Domitz
volumes the right ventricle of normal sub
ject determined by means of
raphy Minerva Med 2:10 1958

20 Thal H C
Nace P F and Jaumet C H Inhalation
radiocard
1958

21 Cronet S and Lagerlöf H O A mathematical
analysis of indicator dilution curves
direct calculation of the
a total volumes of the left ventricle and
and pulmonary blood volume Acta phys
scandinav 36 1956

22 Meier P and Zierler K L On the
tor-dilution method for mea
od flow and volume J Appl Ph

mations of cardiac output an
od me by dye dilution, Phys
19

Van Der Feer and Dorn
theory of cardiac output measure
injection the body Acta card

R F Lewejon F W Jr and
of cardiac output from pre
curves in patients with card
sease Circulation Res 58

W J Pritchard W H, and Mac
The determination of cardiac output
method without arterial sam
Analytical concept Circulation
1958

W J Pritchard, W H and Mac
The determination of cardiac output
n method without arterial sam
Validation of precordial recording
18 114 1958

and Gorlin F S The measure
central circulating blood volume from
dilution curves in normal subjects
patients with mitral stenosis, J Lab &
Med 196 1959

and Hamilton W F
The simultaneous transport of T 1824 and
active red cells through the heart and
Am J Physiol 14 1946

Shaw J E
Adams S Measure
output in the dog by the
of red
cells, Am J Physiol 170
1

Pulmonary red cell and plasma
pulmonary hematocrit in the
normal dog Am J Physiol 12 1946

The pulmonary circulation
time the quantity of blood in the lungs and
the output of the heart Am J Ph vol 20
19

Wells H S
Wilson of the pulmonary
circulation time from the
the femoral artery and
the in the
Invest 28 1949

Wilson and
An a the measure
and of the so-called
the in dilution
Lab Clin Med 41 1953

arterial dilution
Appl Physiol 1954

The
and
1951

Schwartz
output and
pulmonary pattern in mitral stenosis,
Am 1955

38 Gleason W L Bacos J M Miller D E and McIntosh H D A major pitfall in the interpretation of the central blood olume Clin Res 7 27 1959
39 *Lange R Smith C and Hecht H* Skewing of indicator-dilution curves in the arterial system Fed I oc 18 86 1959
40 Blumgart H L and Weiss S Studies on the elocity of blood flow VII The pulmonary circulation time in normal resting individual J Clin Invest 4 399 1927
41 Lagerlof H Werko L Bucht H and Holmgren A Separate determination of the blood volume of the right and left heart and the lungs in man with the aid of the d injection method Scandinav J Clin & Lab Invest 1 114 1949
42 Kraus W L Dock D S Wood and E Haynes F W and Dexter L Determination of pulmonary blood olume in man Fed Proc 18 84 1959
43 McGaff C J Jose A D and Milnor W R Pulmonary left heart and arterial olume in val ular heart disease Clin Res 30 1959
44 Gigli G Donat L Mussman G and Ros R Gli isotopi radioattiv nella determinazione dei tempi di circolo Minerva med 1 1836 19 5
45 Lammerant J and DeVisscher M The determination of mean pulmonary circulation time and pulmonary circulating blood olume in man ith iodinated (I¹³¹) human serum albumin Strahlentherapie Sonderbd 36 128 1956
46 Fich R H Chaffee W R and Chodos R B Measurement of central blood volume by external monitoring Circulation 20 659 1959
47 Rabinowitz M and Rapaport E Determination of circulating pulmonary blood olume in dogs by an arteriovenous dy equilibration method Circulation Res 2 5 1954
48 Nylin G Circulatory blood olume of some organs Am Heart J 34 174 1947
49 Newman E V Merrell M Genecin A Monge C Milnor W R and McKeever W P The dy dilution method for describing the central circulation An analyses of factor haping the time concentration curves Circulation 4 735 1951
50 Kattus A A Rivin A U Cohen A and Sobo G S Cardiac output and central olume as determined by d dilution curves Circulation 11 447 19 5

Case report

Ruptured aortic sinus aneurysm
Case report, with review of clinical features

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With reports during the last 5 years of at least 11 surgical corrections of a ruptured aneurysm of a sinus of Valsalva the diagnosis is no longer one of academic interest alone [1] It is now a matter of paramount importance that the lesion not only be entertained in the differential diagnosis but also that the definitive diagnosis be established with minimal delay

Aneurysms of the congenital variety almost invariably originate from either the right coronary or noncoronary sinus and rupture into the right atrium and or the right ventricle The result is an acute aortic sinus–right heart fistula The characteristic clinical complex usually consists of a young adult without pre-existing evidence of cardiac disease who develops the acute onset of dyspnea and or chest pain The typical signs consist of a murmur in both systole and diastole with maximal intensity about the lower half of the sternum and evidence of rapid aortic runoff

However all of these characteristics are equally typical of a ruptured aortic valve with acute aortic insufficiency which is the most frequent incorrect diagnosis When knowledge concerning pre-existing cardiac disease is lacking and the onset is less dramatic several other lesions might be suggested particularly patent ductus arteriosus and the various congenital defects which occasionally simulate a patent ductus

Although the typical murmurs of these lesions are well known that of an aortic sinus–right heart fistula remains less well defined Agreement exists that the murmur of the typical defect is present in both systole and diastole however there are conflicting reports concerning its exact timing and maximal intensity within the cardiac cycle as well as the site of maximal intensity upon the thorax Phonocardiographic registration of the murmur has been infrequently reported a brief review of the literature revealed only 10 reports in surgically or pathologically proved cases [1-8]

The following case is of interest not only because of the favorable outcome but from a diagnostic viewpoint as well Of special interest are the several symptoms and signs which permitted a reasonably confident diagnosis prior to any laboratory studies and the unusual features of the murmur as confirmed by the phonocardiogram

Case report

J L M a 31 year-old Negro laborer was admitted to The City of Memphis Hospital on Nov 24 1959 with 2-day history of marked exertional dyspnea which was associated with tightness in the upper abdomen During the previous 6 weeks he had noted a nonproductive cough and

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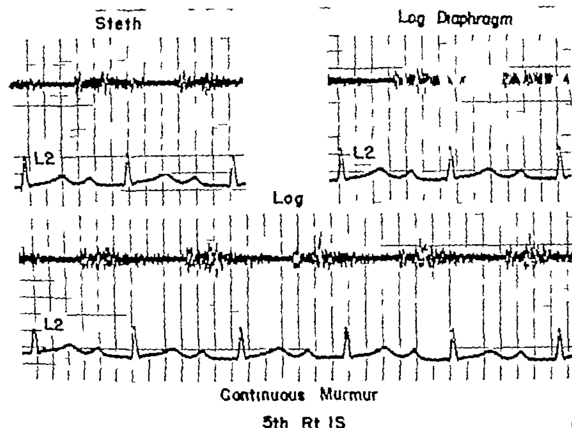


Fig. 1. Phonocardiogram record[ed] at the site of maximal intensity of the murmur. Progressively higher frequency components of the murmur are demonstrated in the stethoscopic, logarithmic, and logarithmic with diaphragm tracings respectively. Note that the murmur is continuous through the first sound and that the peak amplitude occurs just before mid-diastole.

mild pain in the lower left lateral chest which was not influenced by respiration. His only previous admission was 3 years before, at which time an appendectomy was performed. At that time there was no evidence of cardiac disease by physical or chest x-ray examination.

Although he complained of marked dyspnea, he was nevertheless most comfortable in the supine position. The temperature was 98.6 F, the pulse was regular with a rate of 104, and the respiratory rate was 28. The blood pressure was 140/50-0 mm. Hg and the peripheral signs of rapid aortic runoff were evident. The neck veins were moderately distended with suggestion of systolic pulsation. A moderately tender liver was palpable 4 cm. below the right costal margin, and a systolic expansile pulsation was detectable. Moist râles were audible throughout both lungs and there was a trace of pedal edema.

Cardiac examination revealed the apical impulse to be in the fifth intercostal space in the midclavicular line and its character was neither more diffuse nor forceful than usual. Instead, both a slight systolic lift and a diastolic pulsation were visible and palpable in the left parasternal region. An intense thrill limited to diastole was palpable in the fourth and fifth right intercostal spaces parasternally. The first sound was diminished and a moderately accentuated single second sound was heard best in the second and third left intercostal spaces. A marked summation gallop was audible over the midprecordium. A continuous murmur was best heard in the region of the thrill. The diastolic component was Grade 6 in intensity and harsh in quality. It crescendo after the second sound and reached a peak in mid-diastole almost synchronously with the summation gallop; after the peak the murmur became decrescendo through the first sound and systole. The systolic component was Grade 2-3 in intensity with a blowing quality. Both components were also heard less distinctly over the entire precordium. However, the diastolic component was also loudly transmitted to the right and inferiorly and was easily audible in the epigastrium over the liver and at the right anterior axillary line (Figs. 1 and 2).

The ECG (Fig. 3) revealed a first-degree A-V block and a mean QRS axis at 90 degrees. Phonocardiograph confirmed the auscultatory findings (Figs. 1 and 2). Chest x-ray films and cardiac fluoroscopy demonstrated moderate pulmonary congestion with minimal right pleural effusion, slight enl-

Table I Right heart catheterization data

	Blood pressure		Blood oxygen		
	Phasic (mm Hg)	Mean (mm Hg)	Content (ml /100 ml)		Saturation (per cent)
Innominate venous junction	15/10	13	5 6		43
High right atrium	15/10	13	5 9	6 6	45
Low right atrium	13/11	12	6 8		52
Mid right atrium	13/10	11	7 2		55
Apex right ventricle	43/16 (d)	33	9 8	9 9	75
Mid right ventricle†	[illegible]/16 (d)	33	10 7		8[illegible]
High right ventricle	56/5 (d)	31	9 4		72
Pulmonary artery proximal position	54/16	32	9 6	9 5	74
Pulmonary artery	55/7	31	9 4		72
Left brachial artery	110/46 (d)	—	11 8		91
Oxyhemoglobin capacity			13 0		100

Systemic blood flow 6 5 L /min
Pulmonary blood flow 14 8 L /min.
Cardiac index 3 6 L /min /M

O_2 consumed 339 ml /min
Hematocrit 31 vol per cent

*d Damped
†Undamped phasic right ventricular pressure = 55/1 12 mm. Hg
The low systemic arterial oxygen saturation, wide A V oxygen difference and increased systemic blood flow are consistent with high output left ventricular heart failure. The high systemic venous pressure and elevated end-diastolic right ventricular pressure are consistent with right ventricular failure A moderate sized left-to-right shunt into the right ventricle is also demonstrated (The catheterization data were made available through the courtesy of James W Culbertson M D and Sherman H Hoover M D Department of Internal Medicine University of Tennessee Medical Center)

ment of the right atrium and right ventricle and equivocal evidence of increased pulsations of these chambers and the pulmonary artery (Fig 4) The venous pressure was 240 mm of saline and the arm-to-tongue circulation time was 4 second VDRL was negative

Hospital course The working diagnosis was an acute aortic sinus–right heart fistula presumably secondary to a ruptured congenital aortic sinus aneurysm Medical management was attempted with digitalization oxygen and diuretics but this treatment resulted in only temporary improvement. He soon resumed a course characterized by extreme dyspnea on the slightest exertion which was relieved only by his remaining at complete rest in the supine position Several episodes of acute dyspnea not precipitated by effort occurred lasted 30 *to* 60 minutes and then subsided spontaneously

On the second hospital day the patient became febrile and bacterial endocarditis was considered The cause however was soon found to be a perirectal abscess which responded promptly to antibiotics and surgical drainage

On the seventh hospital day a right heart catheterization was performed (Table I) A major rise in oxygen saturation was detected in the right ventricle and was interpreted as indicative of left-to-right shunt with right ventricular exit In addition the right ventricular systolic pressure was elevated to 55 mm Hg

Because of his relentless course an open heart operation during total cardiac bypass was performed on the fourteenth hospital day A continuous thrill was palpable over the inflow tract of the right ventricle A fusiform aneurysmal sac was found to originate from the right coronary sinus and overlap the septal leaflet of the tricuspid valve protruding chiefly into the right ventricle but with a slight bulge into the right atrium The tip of the ventricular portion was ruptured resulting in a fistula which opened into the inflow tract Excision and closure of this ventricular portion produced a rent in the atrial bulge which required an additional atrial incision for closure

Right bundle branch block developed during operation and has persisted since After the operation improvement was prompt and otherwise complete The patient was discharged with neither

*Operation was performed by James W Pate M D Chief Department of Thoracic Surgery University of Tennessee Medical Center

symptoms nor signs on no medications and fully ambulatory. No murmur has since been detectable by auscultation or phonocardiogram. Six months later the patient remained asymptomatic and had returned to work.

Discussion

Differential diagnosis of present case. Previous evidence of a normal heart and the mode of onset of symptoms were of great value in this case, both strongly suggesting that the defect was acutely acquired rather than congenital in etiology. In addition, the presence of a murmur both in systole and diastole associated with signs of rapid aortic runoff further limited the possible considerations and suggested that the defect in all probability originated within the aorta.

Regardless of the more specific etiology (i.e., congenital aortic sinus aneurysm, syphilis, dissecting aneurysm, bacterial endocarditis) the diagnosis of the hemodynamic defect per se essentially resolved to a distinction between acute aortic insufficiency and an acute aortic sinus–right heart fistula. Despite other helpful features, the following two findings were of primary importance in this differential, with both as strongly favoring one diagnosis as they opposed the other. (1) *Absence of significant left ventricular enlargement and failure.* In the presence of marked exertional dyspnea and both cervical vein and hepatic engorgement, several findings directed attention to the right rather than the left ventricle: the absence of orthopnea and actual preference for the supine position, the normal location and character of the apical impulse

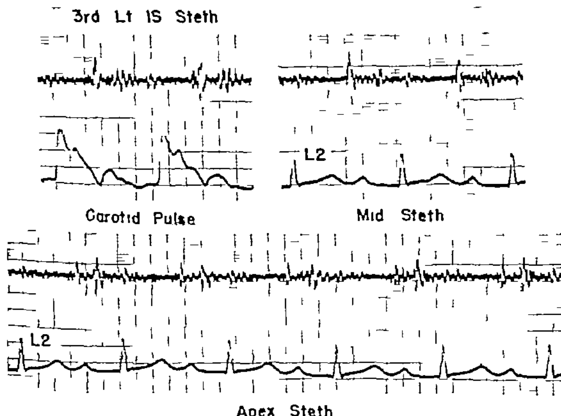


Fig. . Phonocardiogram demonstrating the carotid pulse, accentuated second sound, and the summation gallop. Although the higher frequency components of the murmur can be seen in each tracing, they are of much lower amplitude than those recorded to the right of the sternum (Fig. 1). The second sound is best recorded at the mid precordium and occurs simultaneously with the brief T-P segment. The summation gallop occurs 0.08 second after the summit of the P wave and although easily evident on all three tracings it is most prominent at the apex. The gallop varies slightly in amplitude and number of distinct components, apparently reflecting variations in the degree of summation.

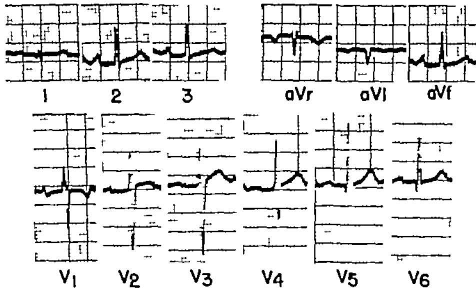


Fig. 3. Electrocardiogram which reveals first degree A-V block (P-R interval of 0.24 second in Lead II) and the mean frontal QRS axis at 90 degrees. In addition late peak evident on the T waves in Leads II, III, and Vr and there is notch on the downstroke of the R wave in Lead V

in contradistinction to the palpatory findings in the midprecordium which suggested a right ventricular systolic lift and diastolic gallop; a mean QRS axis at 90 degrees in a 31-year-old person; asthenic individual; roentgenographic evidence of right chamber enlargement with possible pulsatory phenomenon suggesting that the pulmonary congestion was active rather than passive. (2) *Presence of a continuous murmur.* The continuous character of the murmur was the one feature that was of major importance in this particular differential.

The accentuated pulmonic second sound, first degree A-V block, and the systolic pulsation of the liver and cervical veins were of additional value, although less specific.

Murmur of aortic sinus–right heart fistula. It is probably only rarely that this murmur occurs as an isolated finding. Not only are additional anatomic lesions frequently associated but a variety of relative murmurs unrelated to the actual shunt across the defect are often present. In addition, reported cases of aneurysms of the sinus of Valsalva appear to include a broad spectrum of pathologic entities and encompass almost all diseases known to affect the aortic root and/or aortic valve. For this reason we have attempted to review these heterogeneous reports and offer the following description of the murmur as a composite.

The one constant feature of this murmur is its presence in both systole and diastole. It is usually continuous but not infrequently is composed of separate systolic and diastolic components and resembles a to-and-fro murmur. It is of moderate to great intensity, with the maximal intensity occurring either in both phases or in systole. A thrill is usually associated and its timing corresponds to the maximal intensity. Although only rarely are the maximal intensity and thrill limited to diastole,[23] peculiarities in both the character and transmission of the diastolic component in particular have been described.[1,19,21]

The quality of the murmur is usually harsh or coarse and a "machinery" character is often imparted when it is continuous. It is repeatedly described as having a superficial quality.

The thoracic site of maximal intensity is usually described as "low" and this term is applied in reference to the usual location of a patent ductus murmur. The site is usually between the third rib and the xiphoid and is variously located over or adjacent to either side of the sternum. Transmission of the murmur is generally diffuse. On occa

sion differential transmission of the systolic and diastolic components has been noted with the diastolic component usually directed inferiorly and the systolic component more frequently directed toward the apex.

The characteristics of the murmur have not been of value in determining the specific origin of the fistula within the aortic root. However, the site of maximal intensity of the murmur and the transmission of the diastolic component may provide clues to the location of the exit.[8] When the exit is within the outflow tract of the right ventricle (as reported in cases of syphilis, bacterial endocarditis, and penetrating trauma) the maximal intensity is often higher upon the thorax (second to third intercostal space); when the exit is within the inflow tract of the right ventricle (usually associated with internal aneurysmal sac as in congenital cases) or right atrium, the maximal intensity is usually located lower upon the thorax (third intercostal space—xiphoid). An unusual transmission of the diastolic component to the right and inferiorly has been suggested to be of diagnostic value of a right atrial exit.[19]

The murmur in the present case was continuous with the site of maximal intensity in the fourth and fifth right intercostal spaces parasternally. In this regard it is consistent with that in previous cases in which the fistula enters the inflow tract of the right ventricle through an aneurysmal sac.

However, the transmission of the diastolic component to the right and inferiorly was identical to that previously attributed to a right atrial exit. It would appear therefore that this feature is not quite so specific and that either a right atrial or right ventricular inflow tract exit may result in this unusual transmission.

Of greater interest, however, is the striking maximal intensity during the diastolic phase. The murmur became crescendo after the second sound and reached a peak in mid-diastole almost synchronously with the summation gallop. After this it became decrescendo, passing through the first sound and systole. This is contrary to the description in the majority of reports, and one must speculate that perhaps this diastolic accentuation might be of greater diagnostic value than has previously been recognized.

A general anatomic similarity exists between a coronary artery, a coronary A-V fistula, and the congenital type of the present defect; in essence, they all represent fistulous tracts which originate in the aortic sinuses and usually enter the right heart. These similarities raise the question of whether the flow of blood in the latter two defects might be somewhat analogous to that in the coronary arteries—being maximal during diastole.

It is of interest that this analogy to coronary blood flow has been applied in cases of coronary A-V fistula in which the continuous murmur is not infrequently reported to be maximal during diastole.[20,21] However, whereas both a coronary A-V fistula and coronary artery must traverse the myocardium, the present type of defect consists of an internal aneurysmal sac. Thus, the factor of myocardial relaxation which plays an important role in augmenting coronary blood flow during diastole is not present. Nevertheless, if the exit of the aneurysmal sac is within the right ventricle, a somewhat similar mechanism could conceivably be a factor as a result of the decrease in intraventricular pressure during diastole.

The origin of these three types of fistulae from the aortic sinuses suggests an



Fig. 4. Roentgenogram of chest taken approximately 4 days after rupture of the aortic sinus demonstrating globular enlargement of the heart and acute pulmonary congestion.

additional factor in support of such an analogy Since a Venturi effect may play a role during aortic ejection [7] it is possible that the pressure within the aortic sinuses is disproportionately decreased during systole Since quantitative information about this contribution is not available one can only state what the hemodynamic situation would be if this contribution were sufficient to ensure a maximal aortic sinus pressure during diastole Under these circumstances the maximal flow of a left to right shunt through any of the fistulae would be maximal during diastole this would be independent of whether the recipient chamber were the right atrium or right ventricle

These reflections permit some conclusions concerning the circumstances—in at least congenital types of the present defect—in which a diastolic accentuation of the continuous murmur might occur The combination of an aortic sinus origin and right ventricular exit represent the ideal anatomic situation and the likelihood of such an occurrence would increase with the right intraventricular pulse pressure Should the Venturi effect actually prove to be of major importance a diastolic accentuation might also occur with a right atrial exit however this conclusion must rest upon demonstration of it in future cases

These considerations are of importance in the differential diagnosis of systolic-diastolic murmurs which originate either directly or indirectly from the aorta Such a murmur produced by aortic valvular disease is of course composed of separate systolic and diastolic components The murmurs of patent ductus arteriosus aortic pulmonic septal defect aortic sinus–right heart fistula and coronary A V fistula on the other hand are usually continuous The peak of maximal intensity appears to be of value in differentiating these continuous murmurs The murmurs of a patent ductus or an aortic pulmonic septal defect are usually maximal in late systole or at about the time of the second sound[8] the murmur of coronary A V fistula has frequently been reported as maximal in diastole The present report indicates that a similar diastolic accentuation may be present in cases of aortic sinus–right heart fistula—particularly if the fistula consists of an internal aneurysmal sac within the right ventricle

Summary and conclusions

1 A case of ruptured aortic sinus aneurysm which was clinically diagnosed and surgically corrected is presented The aneurysm was apparently congenital Rupture produced an acute fistula between the right coronary sinus and right ventricular inflow tract

2 The clinical aspects of the case are emphasized particularly the several features which proved to be of considerable diagnostic value

3 The murmur presented several unusual features which were documented by a direct writing phonocardiogram The characteristic murmur of aortic sinus–right heart fistula as ascertained from the pertinent literature is described The murmur of the present case suggests two additional diagnostic points (a) Unusual transmission of the diastolic component to the right and inferiorly may be produced when the exit of the fistula is within the right ventricular inflow tract as well as within the right atrium (b) A diastolic accentuation of the continuous murmur when present may suggest that the origin of the fistula is within an aortic sinus and that the exit is within the right ventricle An analogy to coronary blood flow and the murmur of coronary A V fistula is noted

REFERENCES

1 Lillehei C W Stanley P and Varco R L Surgical treatment of ruptured aneurysms of the sinus of Valsalva Ann Surg 146 459 1957
2 Morrow A G Baker R R Hanson H W and Mattingly T W Successful surgical repair of a ruptured aneurysm of the sinus of Valsalva Circulation 16 533 1957
3 McGoon D C Edwards J E and Kirklin J W Surgical treatment of ruptured aneurysm of aortic sinus Ann Surg 147 387 1958
4 Bigelow W G and Barnes W T Ruptured aneurysm of aortic sinus Ann Surg 150 117 1959
5 Kay J H Anderson R M Lewis R R and Reinberg M Successful repair of sinus of Valsalva–left atrial fistula Circulation 20 427 1959
6 Burn A Evaluation of precordial continuous murmur Rupture of aneurysm of sinus of Valsalva into the right ventricle Am J Cardiol 4 551 1959
7 Lippschutz E J and Wood L W Rupture of an aneurysm of the sinus of Valsalva Am J Med 28 859 1960
8 McKusick V A Cardiovascular sound in health and disease Baltimore 1958 Williams & Wilkins Company

9 Jones A M and Langley F A Aortic sinus aneurysms Brit Heart J 11 325 1949
10 Herrmann G R and Schofield N D The syndrome of rupture of aortic root or sinus of Valsalva aneurysm into the right atrium Am Heart J 34 87 1947
11 Davidsen H G Fabricius J and Husfeldt E Five cases of congenital aneurysm of the aortic sinuses (of Valsalva) and notes on the prognosis Acta med scandinav 160 455 1958
12 Brofman B L and Elder J C Cardioaortic fistula Temporary circulatory occlusion as an aid in diagnosis Circulation 16 77 19 7
13 Abbott M E Clinical and developmental study of a case of ruptured aneurysm of the right anterior aortic sinus of Valsalva Contrib Med & Biol Res II 899 1919
14 Fowler R E L and Bevil H H Aneurysm of the sinuses of Valsalva Pediatrics 8 340 1951
15 Schultz J Coronary arteriovenous aneurysm review of the literature Am Heart J 56 431 1958
16 Steinberg I Baldwin J S and Dotter C T Coronary arteriovenous fistula Circulation 17 377 1958
17 Wiggers C J Physiology in health and disease ed 5 Philadelphia 1949 Lea & Febiger

Clinical pathologic conference

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Clinical abstract

DR SOMERS

First admission

HISTORY A 22 year-old Ganda male on his first admission to hospital gave a history of cough and fever which had lasted 3 months The cough was productive only of scanty white sputum H denied hemoptysis but thought he had lost some weight There was no contact history of tuberculosis

PHYSICAL EXAMINATION H was a normally developed nd reasonably well nourished patient without evidence of recent loss of weight Physical signs were confined to the chest The percussion note was impaired and there were râles and diminished breath sounds over the left lower lobe Clinically the apex beat was in the fifth left intercostal space w thin the mid-clavicular line The heart sound were normal There were no murmurs Blood pressure was 130/90 mm Hg The liver and spleen ere t palpable no lymphadenopathy was evident H did not ppear to be anemic He weighed 105 pounds

LABORATORY EXAMINATION Relevant investigations were as follow hemoglobin 85 per cent (13 3 Gm./100 ml) white blood cell count 12 000/ mm neutrophils 82 per cent lymphocytes 14 per cent monocytes 4 per cent erythrocyte sedimentation rate (Wintrobe) 39 mm /hour The sputum was purulent and on direct examination and culture was show to contain pneumococci Four examinations for acid fast organisms were negati

X RAY EXAMINATION There was shadow of uniform density t the left lung base The left diaphragm was raised nd the left lateral view showed that the opacity involved the lingula pulmonis There w thickening of the transver fissure in the right lung The heart size nd shape ppeared to be normal (Figs 1A and B)

HOSPITAL COURSE A resolving pneumococcal lobar pneumonia was diagnosed and he was tarted on a cour of penicillin.

The fever which was 103 F on dmission ubsided ver the next few day but recurred on the sixth day It was felt that the organism was probably penicillin resista t nd tetracycline was given By the end of the second week the fever had subsided The patie t w discharged w th diagnosis of postpneumonic segmental collapse nd was asked to report for breathing exercises and follow up as an outpatient

When next seen 2 weeks later he still had slight cough Impaired percussion not and diminished breath sound were evident t the left lung base Examinations of sputum for acid fast organisms ere repeatedly negativ Deep breathing exercises were continued nd further course of tetracycline was prescribed A repeat ray examination of the chest showed a moderate increase in the heart shadow (Figs 2A and B) Although reque ted to do so he failed to report again ntil 2 months later hen gain the symptoms nd signs in the chest were essentially unchanged A new sign however was the presence of an enlarged left supraclavicular lymph node Immediate hospitalization was urged but was refused by the patient His wif was imminently expectant and he wished to make rrangements for her deli ery Several weeks later he was readmitted as an emergency case in an extremely ill condition

Second admission On this dmission 6 months after the first there was interv l history of cough productiv of canty amount of white sputum During the 4 weeks previous to admission he had lost weight rapidly The cough had become much worse nd he was breathless and weak The sputum had remained nonpurulent and he denied hemoptysis

PHYSICAL EXAMINATION H was ill wasted patient febrile nd w th moderately severe dyspnea The temperature was 102 F and respirations were 35 per minute Enlarged firm lymph nodes were palpable in both supraclavicular regions left xilla and both inguinal regions

The precordium bulged anteriorly Cardiac d ll ness was continuous w th dullness t the left lung base On the right side cardiac dullness wa noted up to the right mid-clavicular line The heart rat was 140 per minute nd regula Blood pressure

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Fig 1A Posteroanterior roentgenogram of chest taken at first admission.

was 110/80 mm Hg and doubtful pulsus paradoxus (10 mm) as recorded First and second heart sound were audible but they were faint and distant No murmurs were audible The mean jugular venous pressure was raised 3 cm above the sternal angle and pulsations were evident At the left lung base the percussion note was dull and the breath sound were diminished The liver was firm and palpable enlarged 4 fingerbreadths The spleen was not palpable There was no ascites or peripheral edema

ELECTROCARDIOGRAPHIC EXAMINATION The tracing showed regular sinus rhythm with rate of 125 The P wave and P R interval were within normal limits QRS complexes showed low voltage throughout T wave inversion was present in Leads V V and V Others T flat throughout (Fig 3)

HOSPITAL COURSE Pericarditis with effusion was suspected an immediate pericardiocentesis was attempted but no fluid was obtainable The patient condition improved slightly by the next morning but he became very distressed restless and dyspneic 18 hours after admission The venous pressure had increased A repeat pericardiocentesis again yielded dry tap *His condition deteriorated rapidly and* he died a few hours later

Discussion

PROFESSOR WILLIAMS This was a young man with a history of cough and febrile illness and a moderate neutrophilic leukocytosis Since he had a history of illness for 3 months I am surprised that the diagnosis of pneumococcal lobar pneumonia was a confident one because it is rather a long course for this type of pneumonia Clearly in the minds of his physicians there was always the thought of tuberculosis which indeed must have been the thought which came to all our minds in regard to a young man of 22 years with that sort of history slight loss of weight and productive cough Thorough efforts seem to have been made to establish bacteriologic evidence of tuberculosis but results were negative I wonder whether a Mantoux test was made?

DR SOMERS I regret that it was not made Professor Williams

PROFESSOR WILLIAMS He was discharged much improved but there is the point that *the pyrexia had dragged on into the second week* in spite of antibiotic treatment When we look at the x ray films the factor of pulmonary collapse is evident the left diaphragm is very considerably raised although the mediastinum is not displaced So at the time of the first admission there is this history of a rather long illness with considerable pulmonary collapse and little radiographic change 2 months later when he came back with enlarged lymph nodes *This again raises the question of tuberculosis* The patient did not allow any further investigation at that time or one would have been interested in the finding on lymph node biopsy When he came back the third time he was really very ill At



Fig 1B Lateral roentgenogram of chest taken at first admission showing shadow of collapse of left lower lobe



Fig 2A Posteroanterior roentgenogram of chest taken 3 months after admission

this stage I think I would have become rather skeptical about a diagnosis of pulmonary tuberculosis because with this length of duration of the illness and persistent sputum one would by now have expected the tuberculosis to be positive But we have no evidence that acid fast bacilli were ever found He now had much more extensive lymphadenopathy than before and he *had lost more weight If* one withdraws the diagnosis of tuberculosis one must surely consider malignant disease There were now lymph nodes in both supraclavicular regions left axilla and both inguinal regions He had a bulging precordium and increased cardiac dullness He was too ill at this time for further radiography The clinical picture brings out a *new development namely* pericardial involvement with a suspicion of paradoxical pulses and nonspecific low voltage cardiogram with T wave inversion consistent with chronic pericarditis Again there was no biopsy at this stage If it were not for the pericardial presentation one would be thinking of Hodgkin s disease with mediastinal involvement of several months duration and late extension to the peripheral lymph nodes The spleen was not palpable One reaches a provisional diagnosis of malignant lymphoma Carcinoma of the lung is a possibility except for its unlikelihood in a patient of this age and its rarity in African patients There was no pericardial effusion and one wonders why there was so much evidence of pericardial involvement—the huge cardiac shadow the characteristic raised venous pressure the cardiographic signs and paradoxical pulse He could have had a thickened pericardium such as one sometimes sees at a certain stage of tuberculous pericarditis Apart from the lymphadenopathy if he had had a pericardial effusion at some stage one would now have been thinking along the lines of tuberculous pericarditis going on to constrictive pericarditis Instead of this however he started off with a normal sized heart shadow with little or no evidence of effusion and when the heart shadow became large no fluid was found in the pericardial cavity It could possibly be a very thickened pericardium which in the case of tuberculosis can be an inch thick *with caseous tuberculous granulation tissues* having much the same effect on cardiac action as an effusion under tension But usually there would have been an effusion preceding that and here we have



Fig 2B Lateral roentgenogram of chest taken 3 months after admission showing generalized enlargement of the heart shadow Left lower collapse remains unaltered

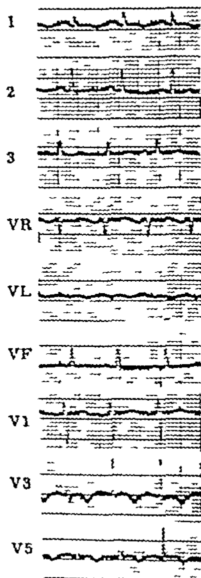


Fig 3 Electrocardiogram taken on last and terminal admission showing low voltage of QRS complexes and T inversion

no such evidence With the extreme wasting and generalized lymphadenopathy one is left with no alternative for a retrospective clinical diagnosis than that of malignant disease of the mediastinum probably malignant lymphoma encroaching on the pericardium There may possibly have been some dilatation of the heart but there seems also to have been a great thickening of the pericardium and it is a question of what type of malignant growth would produce that extensive thickening of the pericardium and at the same time the peripheral lymphadenopathy

That is as far as I can go I leave it that this patient died of malignant lymphoma which originated in the mediastinum

DR O CONOR The anatomic diagnosis was (1) caseous pulmonary tuberculosis left lung with bilateral tuberculous pleuritis—tuberculous empyema left (2) productive tuberculous pericarditis with cardiac fixation and tuberculomata of left ventricular myocardium (3) caseous tuberculous lymphadenitis generalized and (4) caseous tuberculosis of thyroid liver and renals

This patient was found at autopsy to have had a progressive primary type of tuberculosis with a left-sided empyema and a confluent caseous process involving the entire left lower lobe lingula pulmonis and a portion of the left upper lobe There was an associated obliterative fibrocaseous pericarditis and multiple tuberculomata were found in the myocardium of the left ventricle Although there was no pericardial calcification the heart was completely sur



Fig 4 Gross photograph of heart showing extreme pericardial thickening and myocardial tuberculomata

rounded by the productive process which was continuous with a bilateral tuberculous pleuritis Both ventricles were thus fixed rigid and nondistensible (Fig 4)

In addition to the pulmonary and pericardial disease there was active tuberculous lymphadenitis of all major groups in the neck chest and abdomen Gross and microscopic tubercles and caseous masses were found as well in the thyroid liver and both adrenals

Comment

Professor Williams clinical diagnosis is certainly the major differential one in this case We are perhaps oversensitive to malignant lymphoma in Kampala and its high incidence particularly in children and young adults keeps the problem ever in mind

The clinical history and discussion illustrate the difficulty in arriving at a conclusive diagnosis in a specific case and even at the time of gross dissection it is sometimes difficult to make a distinction between lymphoma and tuberculosis in organs and lymph nodes It perhaps therefore calls for a more liberal use of lymph node biopsy in the work up of such a patient particularly when the sputum is repeatedly negative

Diagnosis Tuberculous pericarditis

Electrical axis
Measurement and definition in historical perspective

The QRS and T axis is one of the standard items of clinical electrocardiography. However, in about twenty textbooks of electrocardiography we found in only a few clear definition of and clear instructions for the procedures of determination of the axis. There are some differences in the definition, and the procedure for measurement suggested by some authors is not workable.

One of the most precise definitions and instructions for determination of the mean electrical axis is in the textbook by Burch and Winsor.[1] It (the mean electrical axis) may be defined as the mean electromotive force (magnitude) of depolarization or repolarization acting in an average direction during the period of electric activity. It is a vector quantity in that it has magnitude, direction and sense. It is determined from the algebraic sums of positive and negative amplitudes in Leads I and III plotted on the Lead I and III axes using the triaxial reference system. In the textbook by Graybiel and White determination of the electrical axis from the net amplitude (algebraic sum) in Leads I and III is recommended as the commonly used method (1946). Ashman and Hull[3] also stat that the mean or average electrical axis of the QRS complex is ordinarily determined by the algebraic sum of the amplitudes of R and S in Lead I and III but for the correct determination the net area (algebraic sum of the areas of upward and downward deflections) should be used.

All electrocardiographic textbooks and publications on determination of axis refer to the classic paper by Einthoven, Fahr and De Waart[4] (1913) for the original concept of the electrical axis. However, instead of the term axis these authors used the term direction of the resultant vector (Richtung des resultierenden Potentialunterschiedes) but the term direction is equivalent to the axis. They determined the direction of the maximal instantaneous vector in various conditions by taking the R peak amplitude in two of the three standard leads. They were aware of possible phase differences in the three standard leads. However, they did not suggest determination of the axis from algebraic sums of positive and negative deflections. This was also not done in any of the subsequent publications of Einthoven or his associates and would not have been compatible with Einthoven concept (Fahr[4]).

In the same year (1913) Waller[5] published a paper in which he used the term electrical axis. Probably this is the first time that the term axis was used in the electrocardiographic literature. However, Waller lead and procedure for the determination of axis were different and his publication now is only of historical interest.

Carter[6] probably originated the use of the algebraic sum of the amplitude of positive and negative deflections for measurement of axes. Dieuaide[7] seems to have been the first one to use the term electrical axis in a sense which was consistent with Einthoven original concept.

In 1934 Wilson and his associates[8] introduced the term mean electrical axis defined as the axis of the doublet at the center of Einthoven triangle which develops the mean electromotive force of the heart during the QRS interval. This axis can be determined from the manifest area of the QRS complex of any two of the limb leads. A similar definition was given for the T wave. As a matter of fact the instructions in current textbooks in regard to measurement of area are fairly precise in connection with the determination of ventricular gradient.

However, in the clinical application of the concept mean electrical axis the measurement of QRS and T areas with planimeter or by other techniques is time-consuming and therefore less practical. As mentioned above, the algebraic sum of R and S in Leads I and III, a substitute (although less accurate) for the determination of axis was suggested by Ashman and Hull. The difference in the determinations of axis from the net area and the net amplitude is relatively small for unidirectional and smooth deflections since the correlation between amplitudes and areas is high (for QRS = 0.82, for T = 0.85). The mean T axis can be determined more reliably from the amplitudes than can the QRS axis. However, in diphasic or bizarre QRS or diphasic T the difference may be substantially larger as verified by calculation. Theoretically, the ratio of net amplitude to net area may vary in diphasic deflections quite widely depending on their configuration. The use of amplitudes multiplied by one half of the duration of the deflection may be practically workable, which is close to Schaefer suggestion.[9]

The determination of axis from algebraic sums of deflections is now generally accepted, a large amount of data has been accumulated with this technique, and no change is suggested. However, one should be aware of the limitations of this pro-

cedure nd know that this definition of electrical xis and procedure of measurement does not correspond to Einthoven concept

The axis in Einthoven original concept determined from maximum unidirectional amplitudes has a different meaning t is closely related to the axis of the maximum ector of the QRS and T loops in the frontal plane such plotted by Burch and associates in their ectorcardiographic research [12]

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REFERENCES

1 Boden E Elektrokardiographie fur die arztliche Praxis Darmstadt 1952 Verlag on D Dietrich Steinkopff p 45
2 Burch G E and Winsor T A primer of electrocardiography Philadelphia 1949 Lea & Febiger
3 Graybiel A and White P D Electrocardiography in practice Philadelphia 1946 W B Saunders Company p 458
4 Ashman R and Hull E Essentials of electrocardiography New York 1945 The Macmillan Company
5 Einthoven W Fahr G and De Waart A Über die Richtung und die manifeste Grosse der Potentialschwankungen im menschlichen Herzen nd uber den Einfluss der Herzlage auf die Form des Elektrokardiogramms Arch ges Physiol 150 275 1913
6 Fahr G Personal communication
7 Waller A D The various inclinations of the electrical axis of the human heart Part I The normal heart Proc Roy Soc London (B) 86 507 1913
8 Carter E P Richter C P and Greene C H A graphic application of the principle of the equilateral triangle for determining the direction of the electrical xis of the heart in the human electrocardiogram Bull Johns Hopkins Ho p 30 16 1919
9 Dieuaide F R The determination and significance of the electrical axis of the human heart Arch Int Med 27 558 1921
10 Wilson F N Macleod A G Barker P S and Johnston F D The determination and the significance of the areas of the entricular deflections of the electrocardiogram AM HEART J 10 46 1934
11 Simonson E Schmitt O H Dahl J Fry D and Bakken E E The theoretical and experimental bases of the frontal plane entricular gradient and ts spatial counterpart AM HEART J 47 122 1954
12 Burch G E Abildskov J A and Cronvich J A Studies of the spatial vectorcardiogram in normal man Circulation 7 558 1953
13 Schaefer H Das Elektrokardiogramm Theorie und Klinik Berlin 1951 Springer Verlag

Willem Einthoven
Some historical notes on the occasion of the *centenary celebration of his birth*

The first Edward K Dunham Lectures were given t the Harvard Medical School on October 21 and 22 1924 by Professor Willem Einthoven The title of his lectures was The Relation of the Mechanical and Electrical Phenomena of Muscular Contraction With Special Reference to Cardiac Muscle During hi brief stay in Boston t that time some episodes of historic interest occurred I had never met Professor Einthoven before but inasmuch a the Peter Bent Brigham Hospital was the first hospital in New England to establish an electrocardiographic laboratory and the hospital was only across the street from the Medical School he paid us a isit He and I were seated in the electrocardiographic room chatting about one thing or another when Mrs Bertha Barker our devoted and efficient technician brought in a wet electrocardiographic tracing that she had just taken and developed She interrupted our conversation and asked me whether she should telephone the medical house officer on the wards and tell him that the patient had an acute coronary thrombosis The understanding in the laboratory was that if tracing were taken and showed certain changes with which Mrs Barker was quite familiar she was to telephone the intern directly and not wait until the following morning t 9 o clock when I usually read all the tracings of the previous day When I looked at the electrocardiogram she had just taken I confirmed her diagnosis of acute coronary thrombosis and she left On overhearing this conversation Professor Einthoven w amazed H remarked Do I understand correctly that th lady who is not a physician can make a diagnosis of acute coronary thrombosis from the electrocardiogram without seeing the patient? Apparently he had not as yet become familiar with the work done in the United States on the electrocardiographic diagnosis of myocardial infarction Although the first real publication on the changes in the entricular complex that occur in acute myocardial infarction ppeared in 1920 (Pardee) and was already know to few of the leading cardiologists in Europe it had escaped Einthoven attention When I showed him some

of these tracings he was not only amazed but greatly delighted to learn that the instrument which he had devised had such great practical value.

That same afternoon he attended a tea given in his honor by Dr. Francis W. Peabody in Cambridge. A goodly number of the members of the faculty of the Harvard Medical School were present at this friendly gathering. Someone there, while chatting with him, remarked in a jocular fashion that *he should be getting the Nobel prize for the original valuable and fundamental work he had done in the field of electrocardiography.* He obviously could not make any real reply to this observation and the party continued in *the customary* fashion. I had previously made a dinner engagement with him to dine with me at the Harvard Club in Boston that evening at 6:30.

I arrived at the Club some while before the appointed time and while waiting read the evening newspaper. Suddenly just by chance I ran across an item about Professor Einthoven. Here was a news dispatch stating that he had been awarded the Nobel prize in medicine. When Einthoven appeared I immediately congratulated him on this great and well-deserved honor. He was astounded since he knew nothing about it. In fact, he doubted it. He said that it must be hearsay or gossip which had probably stemmed from the joking that had been going on at the afternoon tea party. He suggested that some newspaper reporter may have *been present there or heard of the whisperings and* casual remarks that were going on in Cambridge. He added that a colleague of his had been congratulated prematurely in a previous year on receiving the Nobel prize as a result of some news that proved to be unfounded. Suddenly he asked me whether the newspaper item I had read was a local report or an overseas communication. I had not paid attention to this point but on quickly looking through the newspaper again I found that it was an *overseas report from* Stockholm. On seeing this Professor Einthoven became convinced that it was valid and naturally was very happy on learning this news. It was not until the next morning that he *received the official cable from* Stockholm which told him about the great award.

So one can say that Einthoven's visit to Boston in October 1924 was memorable in three ways. He gave the first of the celebrated series of the Dunham Lectures. Here he also learned for the first time that the physiologic instrument which he had devised and with which he had established the early fundamental knowledge concerning the electrical impulses of the heart was also destined to be of great value in the diagnosis and care of patients with coronary and heart muscle disease. Finally, it was in Boston that he first learned that he was to receive the celebrated and much honored Nobel prize in medicine.

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Air embolism

The entrance of air into the circulatory system may or may not be fatal depending among other things on the volume of air injected and the rate of injection. It has been estimated that at the same rate of injection the minimal lethal volume of air entering the right side of the heart is seventy times that entering the left side. Sudden death after the entrance of air into the left side of the heart is due to occlusion of the coronary arteries; death also follows occlusion of the cerebral arteries by the same volume of air, but in dogs this occurs only after many hours. So long as the heart can maintain normal arterial perfusion pressure, air will be pushed through the capillaries into the venous circulation. That air under normal systemic perfusion pressure will readily pass the capillary barrier is not generally appreciated.

In the coronary arteries air acts as an effective obstruction even though it can readily be propelled through the myocardial capillaries into the coronary veins. The explanation for this seeming paradox is simple. After injection of air into the left side of the heart, air bubbles are plainly visible in the epicardial arteries. With each cardiac *systole* the proximal part of the intra-arterial air bubble is advanced more than the distal part because of the relative compressibility of air. This dampens systolic thrust and coronary flow so effectively that myocardial oxygenation is impaired. As the myocardium becomes more anoxic the vigor of systolic thrust fails and perfusion pressure rapidly drops to zero. Geoghegan and Lam[a] demonstrated that this sequence of events can be reversed if the coronary arterial pressure is maintained at normal levels. They did this by clamping the aorta and applying cardiac massage, maneuvers impressively simple to employ during thoracic or cardiac operation at which times the hazard of air entering the left side of the heart is well known.

An unexplained phenomenon which regularly follows the embolism of air into any systemic artery is an immediate rise in arterial pressure. The abrupt occurrence of this rise within a few heart beats suggests that it is an autonomic nervous reflex. Teleologically it seems logical that the body would attempt to force the obstructing air through the capillaries. After this initial event, different reactions occur, and in the human forearm it has been demonstrated that arterial air embolism is *followed by* a prolonged period of vasodilatation, the exact mechanism of which is also not understood.

There are some misconceptions in regard to the

cedure and know that this definition of electrical axis and procedure of measurement does not correspond to Einthoven concept

The axis in Einthoven original concept determined from maximum unidirectional amplitudes has different meaning it is closely related to the axis of the maximum vector of the QRS and T loops in the frontal plane such as plotted by Burch and associates in their vectorcardiographic research [12]

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REFERENCES

1 Boden E Elektrokardiographie fur die arztliche Praxis Darmstadt 1952 Verlag von Dr Dietrich Steinkopff p 45
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6 Fahr G Personal communication
7 Waller A D The various inclinations of the electrical axis of the human heart Part I The normal heart Proc Roy Soc London (B) 86 507 1913
8 Carter E P Richter C P and Greene C H A graphic application of the principle of the equilateral triangle for determining the direction of the electrical axis of the heart in the human electrocardiogram Bull Johns Hopkins Hosp 30 162 1919
9 Dieuaide F R The determination and significance of the electrical axis of the human heart Arch Int Med 27 558 1921
10 Wilson F N Macleod A G Barker P S and Johnston F D The determination and the significance of the areas of the ventricular deflections of the electrocardiogram Am Heart J 10 46 1934
11 Simonson E Schmitt O H Dahl J Fry D and Bakken, E E The theoretical and experimental bases of the frontal plane ventricular gradient and its spatial counterpart Am Heart J 47 122 1954
12 Burch G E Abildskov J A and Cronvich J A Studies of the spatial vectorcardiogram in normal man Circulation 7 558 1953
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cian has more recently begun to make judgments about the degree and nature of pathologic changes in the peripheral vascular tree on the basis of pulse waves. A brief evaluation of currently available method for detecting, recording and analyzing these waves seems in order.

Ideally the arterial pressure pulse should be measured by direct connection of an appropriate pressure transducer to a needle or catheter in the lumen of the vessel. Such a system should, when properly chosen, yield an absolute faithful display of the changes in pressure as a function of time. A vast amount of information has been obtained by this approach but unfortunately the trauma involved in direct intra-arterial puncture makes it unacceptable for routine clinical diagnostic purposes. Therefore alternate methods applicable to large groups of individuals have been developed. These indirect techniques generally measure changes in volume or deformations of a single artery, e.g., with a sphygmograph or circumscribed tissue by means of an oscillometer or plethysmograph. Such indirectly obtained curves are not fully acceptable as a substitute for intra-arterial pressure record since there is always the tacit assumption that change in volume of the part is a direct linear function of the change in pressure in some artery. It is unlikely that this assumption is ever entirely valid and probably fails completely under conditions of sclerosis and other modifications of arterial distensibility. Nevertheless empirically such measures of the state of the peripheral circulatory tree have proved to be of great practical value. Curves of this type can be subjected to various analytical techniques to give data that are often of value in clinical problems.

Simple direct, visual inspection of the curves will often permit differentiation between the normal and abnormal. A normal curve obtained with a digital plethysmograph is characterized by a rapidly rising anacrotic limb, a well-defined dicrotic notch and a relatively short crest time. In contrast, in the presence of an arterial obstruction the curve is characterized by a low amplitude, a slowly rising anacrotic limb, rounding of the apex, diminution or absence of a dicrotic notch and a delayed crest time. More sophisticated analyses and comparisons of pulses have been made with mathematical or instrumental adjuncts. In our laboratory four different approaches have been used to analyze a single curve.

1. Differentiating circuits give a direct trace of the *rate of change* of the volume of the part at any time during the pulsations. The derivative curve is highly sensitive and tends to amplify small changes in the primary curve which may not of themselves reveal any visible differences. This technique has detected the presence of disease in individual digits of an extremity as well as cases of unusual sensitivity to nicotine, epinephrine or cold.

2. More exact analyses of an individual pulse curve can be obtained by use of the mathematical technique of Fourier analysis. The complex mathematical operations make it desirable to use proper computers for such analysis. This method determines the characteristic group of sine waves which would be required to build the complex curve obtained from the pulsation. Consideration of the specific frequency, amplitude and phase relationships of these sine waves would provide the basis for a very powerful method. Thus far it has become apparent that arterial obstructive vascular disease results in large changes in the amplitude of high frequency harmonics with large alterations of phase angles. The Fourier analysis may be made more revealing by determining the transfer function which compares the harmonic elements from curves taken at two parts of the body, for example, above and below an obstruction. In this way fine changes in pulse waves produced by vascular abnormalities may be detected.

3. Two pulses may be compared by the simple subtraction of one from another. This can be achieved electrically by subtracting a signal proportional to the volume of one part from that of another. If the two parts are changing in an exactly parallel fashion, the difference curve remains a straight line; if there are even minor differences between the two curves a characteristic pattern is drawn.

4. Vectorplethysmography makes use of a cathode ray oscillograph to compare two simultaneously obtained curves. One curve is placed on the X axis of the scope and the other on the Y axis of the scope, and if the two curves are exactly symmetrical and equal the result is a trace at 45 degrees with the horizontal. Any deviation from identity modifies the line drawn on the scope. With beginning disease the only change in the curve is a modification of amplitude which results in a change in the angle of the vectorplethysmogram on the scope. With moderate disease the pulses recorded from a normal and abnormal extremity differ sufficiently so that the resultant vectorplethysmogram has the form of an open loop rather than a straight line. In advanced disease, when there is some delay in the transmission of the pulse on one side, the open loop takes on a characteristic form in which there is initially a vertical rise or a horizontal deflection before the curve assumes an angular movement. This vertical or horizontal travel is a measure of pulse delay. In addition, the vectorplethysmogram has proved useful in detecting multiple lesions in a single extremity and in localizing, with some precision, the exact point of obstruction in an artery.

Although important clinical information can be obtained from externally recorded volume curves, additional conclusions can be drawn if one considers the local intra-arterial pressures as well. For clinical purposes the auscultatory method or the plethysmographic method of estimating the pressure is satisfactory. For example, with obstructive arterial disease low, rounded pulse curves with delayed crest times and a lack of dicrotic notches are characteristically associated with low systolic and diastolic blood pressures. With a stiff vessel wall the volume curves are of low amplitude but of nearly normal form; rate of rise is rapid, the dicrotic notch may be small and the arterial pulse pressure is wide. A relaxed vessel wall is characterized by volume curves of high amplitude, often with a large dicrotic notch with a normal rate of rise of the anacrotic limb; the arterial pulse pressure is normal or low. With an increase in the cardiac output the externally

recorded olume curves are of high mpl tude and nearly normal form and the rterial pulse pressure high

A careful analysis of pulse waves is of particular clinical alue in discovering the presence and location of ob truction in the arterial tree

Chester Hyman Ph D
Travis W nsor M D
Los A geles Calif

REFERENCES

1 Wiggers C J Circulatory dynamics (Modern Medical Monograph) New York 1952 Grune & Stratton
2 Winsor T Peripheral ascular diseases A objectiv pproach Springfield Ill 1959 Charles C Thomas Publisher p 167
3 Warren J V and Leonard J Intravascular pres ure recording *I* Methods in Medical Research Vol 7 Chicago 1958 Year Book Publishers Inc
4 Lund F Morphological analysis of the digital olume pulse as a diagnostic method Comptes rendus du II Congres i ternational d Angeiologie Fribourg (Suisse) 1 5 Septembre 1955
5 Dontas A S Comparison of simultaneou ly recorded intra arterial and extra arterial pressure pulses in man Am Heart J 59 576 1960
6 Burch G E Digital rheoplethysmography (George E Brow Memorial Lecture) Circulation 13 641 1956
7 Hyman C and Winsor T Application of the segmental plethysmograph to the measurement of blood flow through the limbs of human beings Am J Cardiol 6 667 1960
8 Winsor T and Hyman C Vectorplethysmography J Cardiovas Surg 1 198 1960

Letters to the Editor

Detergent between electrodes and skin

Grand Rapids Mich
November 5 1960

T the Editor

The standard coupling agent between electrocardiographic electrodes and skin is a paste containing glycerin tragacanth and sodium chloride It recommended and sold by manufacturers of electrocardiographs and so far as I h been able to determine is generally used A search of the literature of recent years has failed to turn up any suggestions for a different coupler

The paste is slightly irritating to some skins stick must be washed off usually gets on the operator fingers as he fastens the straps and must be sponged from any clothing or bedding that t touches The electrodes and straps must be washed carefully after each use or sticky residue remains and may corrode metal

The bility of detergent solution to conduct electricity was brought to our ttention by chance Such solution was left in a small sterilizer in which heat is produced by an electric current pas ing through w ter The current was turned on and the fuse in the circuit burned out instantly

So w substituted solution of detergent for the trad tional salt paste on the skin and electrodes and obtained tracings ident cal with those made when used the paste A mixture of one part of liquid detergent in 100 parts of water is pplied w th a dropper to the skin under the raised edge of the electrode in position The chest electrode is dipped in the solution and placed in position on dry skin If there is much hair brushless sha ng cream serves w ll w th suction electrode

When the electrodes are removed ingle wipe w th cleansing tissue is ll that is necessary for the skin Electrodes and straps are also quickly cleaned The total time for the test is ppreciably shortened

Many other ubstances could be used as coupling agents However the wetting and conducting proper ties absence of irritation clea liness od ready av ilability of detergents go far to recommend them for this purpose

The illustration show comparativ tracings

Paul H Knuthers M D

REFERENCE

1 Best C H and T ylor N B The phy olog cal basis of medical practice ed 6 Baltimore Ohio 1955 Waverly Press Inc p 18

P S It has just come to my attention that the *American Journal of Cardiology* published Letter to the Editor from Da id Litt man M D Veterans Admini tration Hospital West Roxbury Mass in which he de cribes the of olutions of salt glycerin propenol and of salt and alcohol These were found to serv ery well

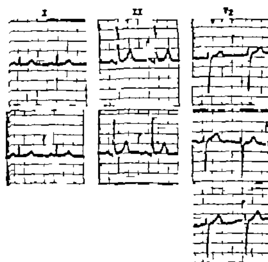


Fig 1 Comparativ tracings *T p row* Detergent on all electrodes *Center row* Paste on all electrodes *Bottom row* Detergent on limb electrodes sha ing cream on chest lectrode

U iversity of Melbourne
Department of Physiology
Melbou ne Australia
November 21 1960

T the Editor

The point that care in deri tion of the ector loops is required especially in relation to phase in the lead tracings is ery importa t and actually underlines an essential precaution in deriving the loops This in itself makes deri tion technical problem electronically and even if it m d perfectly from this aspect cannot yield

formation from the practical standpoint th I ont tned the orig n l surface tion rrents from wh h t is der ed I rthermore differe t frames yield d ff rent der tions The d fficultie in rel tion t the ccept nce of a tandard frame still em in especially when one recog ize th t Vanremoortere (1956) h show th t de rement of potentials in homogeneou yl ndri al me h m m is not complet ly nderstood V tor deriv tion depends on theory which is as y t debate t m them tically for m A tuat l l y the thor tho red resist n the body h ve been recogn zed for a long time and h ve been con idered spe ally by Ka fma nd John ton since 1943 In fa t the conclusion dr wn by them i one of the poi ts indic ting th t th thre d mension l di pl y of Trethewie should be satisf tory in practice

The f t remains th t should ector deri tion be possible w th complet ac ur y wh h en with Schmitt brillia t rese rche is t ll not possible no further nform tion an be deri d from such tors tha is ontained in the orig nal tw dimensional tr ngs Furthermore re ding of such tors is difficult even though this h improv d w th projection to three fl t pl ne

It is desired t stress th t ve tors annot demon trate y f rthe practical nformation than can be obta ned from surface tracings and this ncludes the more recent vidence on heart block nd infarction The d pole concept actually was not rgued but the lectric l sourc t the heart exceedingly compli cated ven if it is regarded as an lmost nf it mber of dipole ppearing nd reappearing specialized sequences and d rections was stre d re ent publication by T thewie (1958)

R Douglas Wright F R A C P
Professor f Physiology

Utrecht Netherlands
September 29 1960

To the Editor

The annotation Electrocardiography by Dr R Douglas Wright (American Heart Journal 60 154 1960) might gi wrong idea of the recent situation of ECG and VCG

The op nion th t such a deriv tion re ts on two f l prem se (p 155) could g e the impression th t th criticism meant for VCG n general A t the first poi t me tioned the pplicability of the dipole conception alu ble work h been done t verify this a sumption Se eral lead systems f VCG t k i to account the eff ct of the position of the d pole The ff ct of the v rying specific resist nce in the trunk wa t ken t accou t many years go As a second point the uthor tates th t different le d system g v differe t result Th f ct ha not been neglected by n estigators in the field of vectorcardiography Opinions ry between the opt mistic view th t the differences are of minor mportance and the more pessimistic view that there is still essential work t be done on this subject But certainly most nvestig tors gree that there re re ons to hoo e one of the systems which hav sound physi cal basis order t avoi l too great a d ergence f t een lead sy tems

The method of Trethewie re ommended by Dr Wright ha some ad ntage ov r the recording of loops and h s been recommended and used by some other thors too The records of the three com ponents of the heart vector can comprise just the same nformation that found n vector loops with t me ma k But this is true only if the phase rel tion b tween the component n be de ived from the records w th sufficie t accuracy It is just one of the adva tages of VCG to g e a result which these ph se diff rences are di played in a way that is adapted to the property of the human brain to recog ize shape The VCG loops give details of shape on such great time scale that it is d fficult to compet with th t in ord ary graphs g ing the components of th heart ve tor as a function of time

The field of ECG including VCG is too vast to be summarized in a single page It is certainly an extremely difficult task t gi a cle r review of the m in point of the recent developments in this restrict d scope I f r that the author h not succe ded in doing so

H C Burger Ph D

Book reviews

Wiederherstellungschirurgie an Herz und Herzbeutel. By Prof Dr Med W Schmitt and Prof Dr Med J Kuda Berlin 1959 VEB Verlag 32 pages 143 illustrations Price DM 36 80

This is a book summarizing the present status of surgical therapy of acquired and traumatic heart disease

The first chapter is by J Kuda about surgical repair of acquired valvular disease cardiac aneurysms and therapy in coronary heart disease It gives excellent description of preoperative diagnostic measures The author's own experience of 1 400 commissurotomies his critical attitude and the inclusion of 300 references make this chapter a valuable contribution to the standard literature

W Schmitt gives detailed description of penetrating heart injuries reports of which he has collected from the literature The clinical symptomatology is discussed and offers good reviews not only to heart surgeons but even more to general surgeons

Foreign bodies of the heart by W Schmitt contain also thorough collection of many cases from the world literature

Diagnosis and therapy of unexpected intraoperative cardiac arrest by Blume includes outline for strict and good therapeutic regimen The undesired hypotensive side effect of procaine amide (Pronestyl) however is not mentioned

Diagnosis and surgical management of pericardial disease with special reference to cardiac tamponade and constrictive pericarditis are discussed by Schmitt

It might be of interest that reference made to great deal of Russian literature

The paper is good but the printing sometimes irregular and the reproductions are not always satisfactory

Atelectasia Pulmonar. By Antonio Jose de Amorim Robalo Cordeiro Second Assistente da Faculdade de Medicina de Coimbra Coimbra 1959 Coimbra Editora Limitada 518 pages

The author's work represents the thesis for the M D degree which was presented at the Faculdade de Medicina de Coimbra

The work is divided into two parts The first one presents the broad problems of pulmonary atelectasis This section contains three chapters (1) Fetal and newborn atelectasis In this chapter the author tries to give detailed presentations of pulmonary embryology followed by his concept concerning the problem of newborn atelectasis (2) Obstructive bronchopneumopathy The etiology and physiopathology of the pulmonary ventilatory defects are summarized and the pathologic aspects evolution and differential diagnosis of the various obstructive bronchopneumopathies are discussed Also described are a great deal of personal experiments performed in laboratory animals (3) Position of atelectasis in pulmonary pathology The main aspects are studied—( ) acquired atelectasis viewed as return to the fetal state and (b) the real magnitude of the problem in medicine

The second part of the work is devoted to circulatory physiopathology of pulmonary atelectasis and is divided into four chapters (1) The author discusses the physiopathology of the pulmonary arterial circulation and bronchial arterial circulation as well as the bronchial circulation and the bronchopulmonary arterial anastomoses (2) With regard to the chapter on clinical investigation and hemodynamics the author contributes 18 cases which have been thoroughly studied (3) In the chapter pertaining to experimental investigation the author describes method for the study of the bronchial circulation and of the bronchopulmonary arterial anastomoses He reviews large number of experiments trying to explain the behavior of the bronchial circulation as related to ( ) pathology of the pulmonary arterial system (b) obstructive bronchopneumonia and ( ) bronchopneumonia in general He ends the chapter with pathogenic and physiopathologic synthesis (4) Final commentary is made on the findings related to the circulatory alteration in the atelectatic lung

The work ends with summary in Portuguese (translated into French and English) conclusions and 909 bibliographic citations

A reading of Dr Robalo Cordeiro's book shows clearly that he has done wonderful work He took up subject which has been thoroughly debated informed himself of nearly everything that had been published up to the present date discussed intelligently the points of view defended by several researchers and tried to make up for the existing lapses

We have an excellent impression of the work The author is extremely careful in his clinical observations strict in his experiences and very cautious in his conclusions We think that his contribution is extremely valuable The work would seem to be very useful to those who wish to broaden their knowledge in the field of pulmonary atelectasis

Pathologie und Klinik in Einzeldarstellungen. Band 8 Klinik der Subakuten Bakteriellen Endocarditis. By Frank Schaub, Oberarzt der Med ... Univer... Berlin 1960 Springer Verlag 207 pages Price DM 49 60

This is a new German language ... on subacute bacterial endocarditis by a ... clinician from the university medical ... It includes a review of the literature ... analysis of personally collected ... 172 cases from the author's own ... other Swiss hospitals Principal emph...

clinical features of the disease and to treatment. There are also short but adequate accounts of bacteriology and pathologic anatomy. The book is well printed and free use is made of tables (of which there are 58) for presentation of relevant statistical data.

To the American physician who reads German, Dr Schaub's monograph offers a comprehensive review of this disease and can be recommended as such. However, this is also true of Kerr's monograph in English. The advantages of the newer work are in the providing of more up-to-date details of treatment and in the careful analysis of well studied large series of recent cases. Perhaps the most important feature of Schaub's work for American readers, and especially for libraries, lies in the abundant references to Continental literature; the reviewer counted 152 for the postwar years. A very interesting change during this time in Europe was the large number of culture-negative cases which appeared in several series, as compared with prewar experience. This sudden increase under disrupted living conditions is strongly suggestive of a different and even contagious causative organism. At least one German worker was led to suspect a viral etiology for these cases. Could many have been examples of the rickettsial subacute bacterial endocarditis of Q-fever described recently in *The Lancet*? The therapeutic implications of this question are very important.

UNTERSUCHUNG UND BEURTEILUNG DES HERZKRANKEN. By Prof Dr h.c. W. H. Knipping, Direktor der Med Univ Klinik, Cologne, and Prof Dr W. Bolt, Doz Dr H. Valentin and Doz Dr H. Venrath, Oberarzte an d. Med Univ Klinik, Cologne. Second edition, Stuttgart, 1960, Ferdinand Enke Verlag. 635 pages, 90 illustrations, 25 tables. Price DM 98.

The first edition of this work (1955) was reviewed in the *American Heart Journal* 1:645, 1956. This is an up-to-date textbook on the diagnosis of heart disease, including catheterization, x-ray kymography, gas analysis and oximetry, angiography, electrocardiography and exercise tolerance tests. The second edition has been enlarged (about fifty per cent), documenting the progress in the diagnosis of heart disease over the past five years. The functional approach, particularly the spirographic analysis in exercise tolerance test, is emphasized. Right and left ventricular insufficiency, pulmonary insufficiency, and combined insufficiency are differentiated with this method. Hemodynamic changes before, during and after cardiac surgery are discussed in detail, including cardiac and respiratory arrest during operations. The equipment of a laboratory for diagnosis of heart disease is described in chapter G (pp 417-446). At the time of the first edition the method of "Isotopen-Ausflutungs-kurven," i.e., decay of radiation of Co^{60} stored in the myocardium, was in the initial phase of development. Since then much experience has been accumulated by the authors and is presented in chapter H (pp 447-461). Age has a significant effect on the speed of decay (slower in older people) and gross differences were found between infarcted and normal myocardium. This method holds much promise for the diagnosis of coronary heart disease but is still in the phase of experimentation.

It is of course impossible to give equal representation to all methods which are used in the diagnosis of heart disease without considerable enlargement of the book. Electrocardiography, for instance, cannot be adequately presented in 20 pages, nor ballistocardiography in 3 pages.

The authors go beyond the diagnosis of heart disease; questions of etiology and environmental factors are also considered, and particularly exercise therapy. Here the experience of the authors is quite unique (extending over 30 years). Work tolerance is of course a fundamental consideration in the management of patients with heart disease, and the book provides much valuable information not easily obtainable elsewhere.

Announcement

A COURSE IN CARDIOLOGY (rheumatic fever, rheumatic heart disease, and congenital heart disease) for general physicians and specialists, sponsored by the Michigan Heart Association and the University of Michigan Medical Center, will be given March 15-17, 1961, at the University Hospital, Ann Arbor, Mich.

In addition to a number of eminent speakers from the state of Michigan, the following guest lecturers will participate: Richard J. Bing, M.D., Detroit; S. Gilbert Blount, M.D., Denver; Eugene W. Braunwald, M.D., Bethesda; Jesse E. Edwards, M.D., St. Paul; Earl B. Kay, M.D., Cleveland; John Kirklin, M.D., Rochester, Minn.; George Murphy, M.D., New York; Charles H. Rammelkamp, M.D., Cleveland; Will Sealy, M.D., Durham; Gene H. Stollerman, M.D., Chicago; and May G. Wilson, M.D., New York.

For further details write to Dr. John M. Sheldon, Director, Department of Postgraduate Medicine, University Hospital, Ann Arbor, Mich.

American Heart Journal

April 1961 Volume 61 Number 4

Editorial

Coronary atherosclerosis Status of MER 29 (triparanol)

*A C Corcoran M D**
Cleveland Ohio

Various epigrams attempt to characterize man He is a social animal but he shares this propensity with the rat and other species He is a rational biped but he often acts irrationally Homer Smith gets closer to a definition by describing him in terms of highly developed consciousness It is this and its corollary the ability to reflect that makes him the supremely expedient animal Confronted with a problem he solves it gets around it or rationalizes it often thereby creating new problems so that the process repeats indefinitely Thus faced with heavy loads and a weak back his strong mind invented the wheel The wheel led him to make roads roads led to the invention of the horse collar and of wagon springs and ultimately to the automobile with all its attendant hazards

Some of these expedients and solutions have been unexpectedly disadvantageous Thus thanks to human ingenuity a powerful and vocal part of mankind enjoy the more abundant Life and is both sedentary and overfed The snake in this greasy garden is the high prevalence of coronary atherosclerosis with its sequelae of arteriosclerotic heart disease and myocardial infarction in young men and middle aged men and women As a nation we feel this more than most However the problem arises in every group capable of relatively easy living Perhaps our economists could get better insight into the relative status of a country such as Russia from statistics on coronary heart disease than from estimates of production of commodities

We do not seem to recognize the fact that we have rational if incomplete solutions to this great social problem nor do we act on this knowledge As Olson has pointed out we know as much about the real causes of coronary atherosclerosis as we do about tuberculosis Koch s postulates have been fulfilled and if we still cannot explain many cases of coronary heart disease it is also true that we cannot explain every case of tuberculosis Physical exercise tends to prevent or delay atherogenesis[1] the prevalence of coronary atherosclerosis increases with the use of diets rich in calories especially fat calories and particularly most hard fats Indeed diet and exercise seem to be largely two sides of the same coin Skeletal and heart muscle use more fatty acid for energy than they do carbohydrate and if diet

F[illegible] Departm[illegible] f Cl[illegible] [illegible] Cl[illegible] Hospital Cleveland Ohio
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*[illegible] Research F[illegible] [illegible] Heart I[illegible] (HF [illegible]) [illegible] of Health Department of Health, Ed[illegible] [illegible] W[illegible]

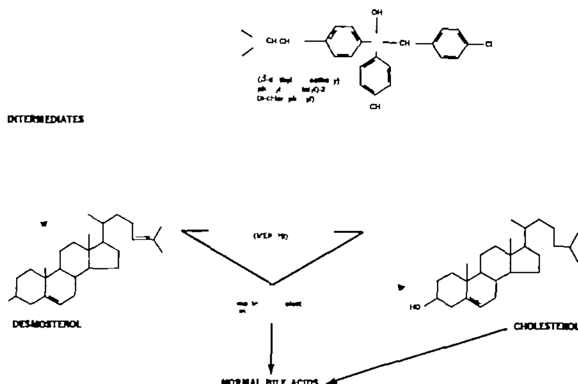


Fig *1* Schema illustrating structure and action of MER 29

provides more fat precursors or stress mobilizes more fatty acid than the muscles use the excess fat circulates preferentially in the beta lipoproteins Then assuming the filtration concept of atherogenesis[7] some of these fragile and bulky molecules decompose in the intima as plasma filters through The soluble protein and miscible phosphatide fractions move on fat and cholesterol accumulate the tissue reacts and atherogenesis begins

Of course this is an oversimplification Heredity anatomy arterial pressure emotional and endocrine status and nonlipid dietary factors all have to be considered Correspondingly the report on diet and atherogenesis recently released by the American Heart Association[8] includes many reservations Nevertheless much more directly than its predecessor[9] it does recommend reduction or control of fat consumption under medical supervision with reasonable substitution of polyunsaturated for saturated fats as a possible means of preventing atherosclerosis The recommendation applies specifically to coronary atherosclerosis There is little or no evidence to suggest that diet or exercise bear on the genesis of aortic atherosclerosis These may be distinct entities linked by misleadingly similar lesions

If we were not so given to expedients the way would be clear In order to prevent or delay most coronary atherosclerosis we should begin systematic programs of diet and exercise in youth and continue these through life Unfortunately asceticism is more admired than practised The search for medicinal expedients began years ago The first was iodide Given to rabbits in doses that cause iodism in man it delayed atherogenesis by impairing their appetite for fat and cholesterol diets It may have had some specific antiatherogenic effects related possibly to formation of thyroid analogues with small fleeting oxidative and large lipopenic effects Soya lecithin was advocated it is moderately distasteful fairly bulky suppresses appetite and provides unsaturated fat Recently unsaturated fat has been used as such it also inhibits appetite and isocalorically substituted for saturated fat lowers the level of serum lipid and cholesterol More practical but more appetizing is substitution of unsaturated for saturated fat in palatable

normal diets Lipocaic among other agents may have some effect on transport of fat and injected heparin certainly has Another approach is to impair intestinal absorption of cholesterol directly as with sitosterol or indirectly by sequestering cholic acid [11] again with the requirement of bulky before meal medication Lastly large doses of nicotinic acid often depress serum cholesterol The mechanism of this action is not clear liver damage has been described and effective doses usually provoke distressing side effects of flushing and pruritus In brief none of these expedients is really convenient

The ideal would be an agent that in small doses would specifically decrease availability of cholesterol for beta lipoprotein synthesis Among agents tested phenyl propionic acid has this effect on liver slices the data are not convincing that it has hypocholesterolemic effect in vivo A much more regularly effective agent was thoroughly discussed at a conference held in December 1959 [1] This compound MER 29 (triparanol) inhibits saturation of the C_{24} C_{25} double bond (Fig 1) The inhibition results in a new body sterol equilibrium in which the immediate precursor of cholesterol desmosterol substitutes for some of the cholesterol of blood and non neural tissues If substitution were all that occurred and if desmosterol were as atherogenic as cholesterol—so far no one knows whether it is or is not—the compound might be only of academic interest What makes it important is that accumulation of desmosterol seems to slow down synthesis of *its* precursors so that the total body sterol pool decreases The dynamic equilibrium of cholesterol then tends to deplete cholesterol from storage sites including experimental atheroma

The remarkable thing is that this depletion seems to occur clinically in patients with arteriosclerotic heart disease This has not been directly demonstrated except that regression of xanthelasma in a hypercholesterolemic patient given MER 29 suggests that it may occur (Fig 2) However studies of more than 1 year s duration at the time of the Conference and more than 2 years now indicate that a substantial proportion of patients with angina pectoris improve with reversion toward normal of electrocardiographic changes in some and decreases in serum cholesterol and lipid in most especially in those initially hyperlipemic Of course angina is a difficult thing to evaluate It can improve spontaneously it is highly conditioned by emotions and suggestions nitroglycerin requirement is a more or less dubious datum even exercise tolerance tests may be misleading measures of changing status Hence the impact of the evidence lies more in its mass and direction than in any single criterion that proves what indirect evidence suggests is regression of atheromata

Few undesirable side effects were described at the Conference For the most part these were rashes and gastric irrita



Fig 2 Equal magnifications of xanthelasma of the left eyelid before (above) and after (below) 6 months of treatment with MER 29 The serum cholesterol before was about 300 and during treatment about 160 mg per 100 ml

tion in about the proportion that would occur from taking aspirin. The manufacturer's current estimates indicate that these occur in less than 2 per cent of patients. Specific toxic effects were not observed even when the dosage was increased to as much as 10 times the usual 250 mg. daily. Large doses do not further impair hepatic function in patients with liver disease, although they may have little effect on the low levels of serum cholesterol in these patients.[13] In this respect, MER-29 differs substantially from Benzmalecene, an agent that interferes with the acetate conjugations that are the first steps in cholesterol synthesis. Since such conjugations underlie many other important reactions, it is not surprising that the drug was unpleasantly hepatotoxic.[14] Thus the low toxicity of MER-29 is a result of its acting only on the last step in cholesterol synthesis. Recently, very large doses of MER-29 have been reported to impair adrenal cortical response to ACTH,[15] possibly by limiting the available supply of adrenal cholesterol. However, among patients taking the drug in doses of 250 or 500 mg. daily for months or years, signs of deficient adrenal function have not been recognized.

MER-29 was marketed about a year ago and with a vastly better background of basic and clinical study than most agents, including, for example, sulfanilamide. Physicians' opinions as to its effectiveness vary. Some whose first patients responded well are enthusiastic; some have been disappointed by transient responses, and others discouraged by examples of resistance. The lack of unanimity is understandable because few physicians can provide truly adequate pretreatment and post-treatment data from sufficient numbers of patients to formulate definite *opinions based on personal experience.* Some may start the drug shortly after a myocardial infarct has already altered serum cholesterol,[16] and some give it with other possibly hypocholesterolemic agents or they may restrict or, more often, relax dietary control at the time it is prescribed.

The proportion of patients who respond by a decrease in serum cholesterol is usually described as 1 out of 5. A preliminary review of our experience with Dr. Henry Zimmerman suggests that it is closer to 3 out of 5. However, this experience includes 20 hospitalized patients whose courses of observation averaged only 2 weeks, some of whom had recent myocardial infarcts, and 50 office patients whose course of observation by Dr. Zimmerman averaged 6 months. Of these 50, 27 showed definite (more than 10 per cent decrease) and 5 doubtful responses; 2 of the nonresponders did respond when dosage was increased to 500 mg. daily; 3 had low levels of serum cholesterol to start with, and 7 were on heparin at the time treatment was started. Most of the patients had asymptomatic arteriosclerotic heart disease to start with and felt neither better nor worse as a result of treatment. Some described a feeling of well-being which may have reflected their conviction that they now saw a way out of a seemingly hopeless situation or their relief at relaxation of strict dietary control. A few seemed to be actually improved. Thus, a woman with essential hypercholesterolemia whose serum level fell from 750 to about 400 mg. per 100 ml. on 250 mg. of MER-29 daily described disappearance of angina; interestingly, this recurred at a serum cholesterol of 250 mg. per 100 ml. when 4 mg. of dextro-thyroxine was added to her regimen. A personal communication from Dr. Jorge Martins de Oliveira of Rio de Janeiro describes relief of angina in 25 of 30 patients under treatment. In 6 this was associated with electrocardiographic improvement; group means of serum levels of cholesterol and beta lipoprotein decreased, whereas alpha lipoprotein increased. Neither Dr. Zimmerman's nor Dr. Martins' series indicated the appearance of major side effects attributable to the drug.

Webster's New World Dictionary lists two meanings of the term *expedient*, i.e., something useful for effecting a desired result, or based on or offering what is of use or advantage rather than what is right and just. In brief, an expedient must be effective and it may be either good or bad. Possibly the procedure best directed toward delaying onset of coronary arteriosclerosis would be a wholesale, fairly drastic change in exercise and dietary patterns from youth on. But this might be

injurious to some and ineffective in most if it were vigorously and indiscriminately applied to people of middle age some of whom have already significant arteriosclerotic heart disease Certainly these people do require reasonable individualized acceptable hygienic guidance Many need more than this especially those who are hypercholesterolemic i e those who have a serum cholesterol over about 240 mg per 100 ml For most of these MER 29 seems to be fairly effective and to use the moral judgment right and just and therefore the best simple expedient available What the drug can do by itself toward preventing coronary atherosclerosis we will not know until systematic longitudinal surveys have compared prevalences of arteriosclerotic heart disease in large numbers of control and treated subjects over several years

REFERENCES

1 Zinsser H Rats lice and history Boston 1935 Little Brown and Co
2 Smith H W The biology of consciousness in the historical development of physiological thought edited by Chandler M Brooks New York 1959 Hafner
3 Olson R E Diet and coronary artery disease Circulation 22 453 1960
4 Morris J N and Crawford M D Coronary heart disease and physical activity of work Brit M J 2 1485 1958
5 Keys A Diet and the epidemiology of coronary heart disease J A M A 164 1912 1957
6 Rothlin M and Bing R J Extraction of individual fatty acids by the heart (Abstract) J Lab & Clin Med 56 94 1960
7 Page I H Lewis Connor Lecture Atherosclerosis An introduction Circulation 10 1 1954
8 Report by the Central Committee for Medical and Community Program of the American Heart Association Dietary fat and its relation to heart attacks and strokes Circulation 23 133 1961
9 Page I H Stare F J Corcoran A C Pollack H and Wilkinson C F Atherosclerosis and the fat content of the diet Circulation 16 163 1957
10 Brown H B and Page I H Variable responses of hyperlipemic patients to altered food pattern J A M A 173 48 1960
11 Tennent D M Siegel H Zanetti M E Kuron G W Ott W H and Wolf F J Plasma cholesterol lowering action of bile acid binding polymers in experimental animals J Lipid Res 1 469 1960
12 Conference on MER 29 (Triparanol) Irving S Wright Chairman Prog Cardiov Dis 2 No 6 (Part 1 May) 1960
13 Raskin A The hypocholesterolemic effect of triparanol (MER 29) in man A M A Arch Int Med 106 803 1960
14 Page I H and Schneckloth R E Hypocholesterolemic effect of Benzmalacene Circulation 20 10 5 1959
15 Melby J C St Cyr M and Dale S L Reduction of adrenal steroid hormone production in healthy adults and patients with hyperadrenalism by an inhibitor of cholesterol biosynthesis New England J Med (In press)
16 Dodd Sir C and Mill G L Influence of myocardial infarction on plasma lipoprotein concentration Lancet 1 1160 1959

Clinical communications

Contributions to the functional morphology of the P wave

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Technical progress has greatly facilitated a more detailed analysis of the P wave by means of scalar electrocardiography (high fidelity electrocardiography[1]) and by electrical dissection of the vector cardiogram (differential vectorcardiography). Notwithstanding, the conventional electrocardiogram still supplies a major amount of information on this wave. Much effort has been expended on increasing our knowledge of atrial activity. The original but laborious method of Abildskov[2] for the study of atrial activation and the simple but practical criteria of Macruz and associates for the recognition of atrial enlargement serve the same purpose.

In the present study, using the conventional electrocardiogram, some morphologic particularities of the P wave have been investigated by methods not previously employed.

The normal peaked P wave and especially its pathologic counterpart present a triangular shape the angles of which can be easily and accurately measured. With certain limitations the same method can also be applied to the study of the rounded P waves. Therefore, the angular structure of the normal P wave was investigated and its correlation with cardiac rate and with age was established. The concept of rising time and rising velocity in normal subjects has been established.

The electrocardiographic pattern of pulmonale P wave was investigated by means of these new criteria in patients with chronic cor pulmonale. Acute pulmonale P was produced experimentally by breathing against manometric pressure and was analyzed in detail. Finally, the ratio of Macruz was systematically investigated in normal subjects and in subjects with chronic and experimentally produced acute right atrial overload, and its diagnostic value was critically assessed.

Methods and material

The conventional electrocardiogram recorded by a Sanborn Instomatic electrocardiograph with the subject in the recumbent position was used in the present study. According to the shape of the P wave, records were divided into two groups: those with peaked and those with rounded apex. For exact quantitation a magnifying lens was constantly used. A peaked P wave was considered to be present when the sharp pointed apex lasted not more than 0.01 second. Any other P waves with a longer lasting apex with rectilinear or curvilinear configuration was considered to be rounded. All measurements were made in Lead II only. The height of the P wave was measured in millimeters from the upper level of the base line to the peak of P. Duration of the P wave was determined from the onset of the P wave to the onset of the P-R segment. The P-R interval was measured from the onset of the P wave to the onset of the QRS complex and expressed in hundredths of a second. Duration of the P-R segment was calculated by substracting the length of the P wave from the length of the P-R interval. The surface

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area of the P wave was calculated by multiplying height with duration and then dividing this sum by 2. The result is expressed in microvolt seconds (mvs). The rising time was determined (Fig. 1) by measuring the length of the projection of the ascending limb of the P wave on the base line. For this purpose a vertical line was dropped from the apex and the distance from the onset of the P wave to the intersection of the vertical with the base line was measured and expressed in hundredths of a second and as a percentage of the duration of the P wave. The rising velocity of the P wave was calculated by dividing the height of the P wave by the rising time and was expressed in millimeters per 0.01 second.

All these definitions refer to the peaked P waves, the exclusive subject of the present study.

The index of Macruz was calculated by dividing the duration of the P wave by the length of the P-R segment as described previously.

Of the angles which form the atrial triangle only angles α and β were measured directly, whereas angle γ was calculated according to the formula $\gamma = 180° - (\alpha + \beta)$. The ascending and descending limbs of the peaked P wave in normal cases and especially in cases with abnormally increased height can easily be extended by using a ruler. The angle formed by the lines of prolongation of the limbs of the P wave with the horizontal lines of the electrocardiographic record can be accurately measured by a goniometer.

For the study of experimentally produced acute pulmonary P the following method was used (Gross[6]). After the conventional electrocardiogram had been recorded with the subject in the decubitus position, an ordinary blood pressure apparatus was placed on a table at the side of the recumbent subject and at the height of his line of vision, so that he could observe the movement of the column of mercury during the performance of the test. Cuff connection of the apparatus was removed and replaced by a rubber tube 50 cm. in length provided with a convenient glass mouth piece. The subject was instructed to blow after a deep inspiration into the tube connected with the manometer so as to elevate the column of mercury above 60 mm. and to sustain it for 15 seconds.

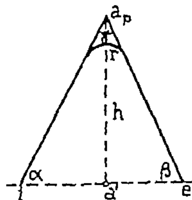


Fig. 1. The angular structure of the P wave and geometrical representation of the rising time and rising velocity. a_p, Apex of the peaked P wave. a, Projection of the apex on the base line. a-e, Rising time. h/rising time, Rising velocity. a-e, Fall time. r, Summit of the rounded P wave.

The correlation between the P wave and different cardiac rates was studied in groups each containing 30 records from 51 to 110 beats per minute. Average values were calculated in each group. The correlation between the P wave and age was studied in three groups. The young age group comprised subjects under 20 years of age, the middle-aged group, subjects between 21 and 50 years of age, and the old age group, subjects over 51 years of age.

Results

Normal peaked P wave. Table I reproduces all the corresponding measured data.

Correlation between normal peaked P wave and cardiac rates (Table II). According to the observed data, cardiac rates cause change in the morphology of the P wave in a certain sense, but there is a lack of strict quantitative parallelism.

Correlation between normal peaked P wave and age (Table III). The influence of age on the morphology of the P wave is very definite. The height of the P wave decreases but its duration and surface area increase with increasing age. The rising time increases and the rising velocity decreases very clearly with advancing years. The duration of the P-R interval is prolonged. Angle α decreases progressively, whereas the apical angle γ enlarges with increasing age. The index of Macruz also increases

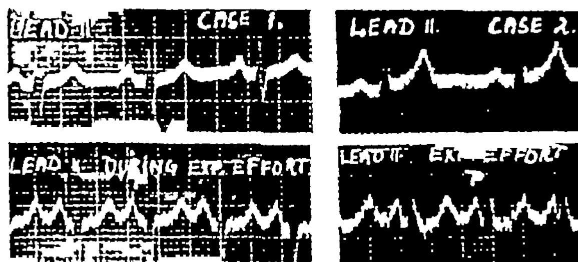


Fig. 2. Characteristic changes observed in two cases.

Cardiac patients presenting pulmonary P pattern (*Table I*). The pulmonary P wave in Lead II is 86 per cent higher, of equal duration, discloses a surface area 77 per cent larger than the normal P wave, presents a 3 per cent shorter rising time and a rising velocity 82 per cent greater than the normal P wave. The P-R interval remains unaltered. The ratio of Macruz increases by 12 per cent. Both angles of the base of the atrial triangle increase: angle α by 38 per cent and angle β by 31 per cent. Consequently, angle γ decreases by 38.5 per cent.

Healthy subjects presenting experimentally produced acute pulmonary P wave. Fig. 2 shows tracings that very distinctly exhibit all the characteristic changes observed in this test.

CASE 1. Healthy male subject, 43 years old. The resting electrocardiogram presented normal sinus rhythm with 83 beats per minute. The P wave was 1.4 mm. in height, 0.11 second in duration, and its surface area measured 7.7 mvs. The rising time was 0.06 second that represented 55 per cent of the duration of the P wave. The rising velocity measured 0.35 mm. per 0.01 second. Duration of the P-R interval was 0.17 second and the index of Macruz was 1.83. Angle α measured 48°, angle β 65°, and angle γ 67°. The electrocardiogram registered during expiratory effort revealed a cardiac rate of 128 beats per minute, i.e., an acceleration of 41 beats per minute (+49 per cent). The acutely pointed P wave presented a height as great as 3.0 mm. (+114 per cent) and a duration of 0.10 second (−9 per cent). The surface area measured 15.0 mvs (+94 per cent). The rising time was 0.04 second (−43 per cent), representing 40 per cent of the duration of the P wave. The rising velocity increased to 0.43 mm. per 0.01 second (+23 per cent). Duration of the P-R interval shortened to 0.14 second (−18 per cent). The index of Macruz increased to 2.5 (+37 per cent). Angle α measured 60° (+25 per cent), angle β 72° (+10 per cent), and angle γ 48 (−29 per cent).

CASE 2. Young man, 30 years old. The resting electrocardiogram showed a regular sinus rhythm of 71 beats per minute. The height of the P wave measured 1.0 mm. and the duration was 0.10 second. Consequently, the surface area was 5.0 mvs. The rising time measured 0.045 second, 45 per cent of the duration of the P wave. The rising velocity was 0.25 mm. per 0.01 second. The P-R interval measured 0.16 second in length. The index of Macruz had a value of 1.66. Angle α was 55°, angle β 64, and angle γ 61. During expiratory effort the following alterations were observed: Cardiac rates increased to 107 beats per minute (a difference of 36 beats, +50 per cent). The height of the P wave increased to 3.2 mm. (+220 per cent) and lasted 0.08 second (−20 per cent). Therefore, the corresponding surface area measured 12.8 mvs (+156 per cent). The rising time increased to 0.06 second (+33 per cent), and

the rising velocity to 0 53 mm per 0 01 second (+112 per cent) The P R interval was 0 12 second in length (−25 per cent) The Macruz index was 2 0 (+20 per cent) The angle α was then 60 (+9 per cent) angle β 83° (+29 per cent) and angle γ 37° (−40 per cent)

Table IV contains all pertinent data observed in this group of 15 subjects As a conclusion we may state that expiratory effort caused acceleration of the heart rate by an average of 35 beats per minute The height of the P wave increased by 48 per cent its duration shortened by 17 per cent and its surface area increased by 91 per cent The rising time was prolonged by 22 5 per cent and rising velocity increased by 73 per cent The P R interval was shortened by 17 5 per cent The index of Macruz increased by 17 per cent The basal angles of the atrial triangle α and β increased 27 and 28 per cent respectively and the apical angle γ decreased by 38 per cent

Discussion

The morphogenesis of the P wave is settled almost satisfactorily Opinion is unanimous that the ascending limb of the P wave corresponds to the activation of the right atrium Septal activation correlates with the inscription of the ascending segment of the P wave Left auricular activation is related partly to the ascending portion and partly to the middle and lower third of the descending portion of the P wave This correlation refers to the conventional Lead II where all morphologic particularities of the P wave are most clearly present Correlation of the rounded P wave to atrial activation is more speculative in the present study the investigation is limited exclusively to the peaked P waves as inscribed in Lead II

The magnitudes of the normal P wave observed in this study are in perfect accordance with general experience The height of the P wave—1 24 mm ± 0 42 (0 5 to 2 5 mm)—is of the same order of magnitude as that indicated by Ashman and Hull[8] i e 1 25 mm (0 3 to 2 5 mm) by Sano and associates i e 1 3 1 4 mm (0 5 to 2 5 mm) and by Stewart and Manning[9] i e 1 4 mm ± 0 53 The duration of the P wave was 0 097 second ± 0 014 (0 06 to 0 12 second) whereas the corresponding values indicated by other authorities were 0 09 second ± 0 015 (0 07 to 0 12 second) by Sano and associates and 0 09 second (0 06 to 0 11 second) by Macruz and associates[4]

The height of the P wave indicates the

Table I The linear and angular structure of the peaked P wave in normal condition and in chronic cor pulmonale

	Age (yr)	Rate (min)	Height (mm)	Duration (sec)	Surface area (mm²)	Rising time sec	Rising time %	Fall time (sec)	Rising velocity (mm /0 01 sec)	P R (sec)	Angle α	Angle β	Angle γ
						Normal							
Mean	43 5	80	1 24	0 097	5 97	0 0512	53 3	0 0448	0 260	0 16	44 0	51 5	84 5
S D			0 42	0 014	18	0 0137	10 3	0 0115	0 111	0 0 2	9 6	10 3	19 7
Range	8	51	0 5	0 06	4	0 07	25 0	0 0	0 100	0 12	20 0	22 0	41 0
	8	110	2 5	0 12	14 4	0 08	80 0	0 08	0 750	0 2?	77 0	73 0	122 0
						Chronic Cor Pulmonale							
Mean	52 0	86	2 31	0 096	10 56	0 05	51 7	0 046	0 475	0 157	60 7	67 3	57 0
S D			0 36	0 014	2 33	0 013	9 8	0 0095	0 15?	0 022	8 7	6 0	11 5
Range	22	54	1 6	0 08	6 4	0 03	37 0	0 03	0 170	0 1	41 0	41 0	29 0
	68	110	3 0	0 12	15 6	0 05	67 0	0 09	0 7 0	0 22	75 0	75 0	81 0

Table II Correlation between normal peaked P wave and cardiac rates (average values)

Cardiac rate (min)	Height (mm)	Duration (sec)	Surface area (mms)	Rising time		Fall time		Rising velocity (mm /0 01 sec)	P R (sec)	Macruz index	Angle		
				sec	%	sec	%				α	β	γ
51 60	1 06	0 095	4 99	051	53 8	014	46 4	0 220	0 168	1 30	41 9	46 6	91 5
61 70	1 03	0 095	4 91	055	57 5	010	42 5	0 182	0 158	1 50	39 8	46 1	91 1
71 80	1 31	0 102	6 60	050	49 6	052	50 5	0 289	0 159	1 79	46 6	51 8	81 6
81 90	1 42	0 096	6 77	052	54 2	014	45 9	0 283	0 152	1 71	45 9	55 6	78 5
91 100	1 26	0 093	5 82	045	48 5	048	51 5	0 306	0 158	1 43	45 1	52 7	82 2
101 110	1 43	0 093	6 72	053	56 1	010	43 6	0 283	0 163	1 32	45 0	55 2	79 8

magnitude of electrical potential produced during atrial activation and the time interval required for its development measured from the onset of the P wave up to its maximal expression is called the rising time of the P wave The average duration of the rising time in subjects with normal P waves measures 0 0512 second ± 0 0137 that represents 53 3 per cent ± 10 3 of the duration of the P wave On the other hand the rising time represents geometrically the length of the projection of the ascending limb of the P wave on its base line Therefore its relative duration indicates that the normal peaked P wave is built slightly asymmetrically because the projection of its peak on the base line is deviating to the left of the center by 3 3 *per cent*

The rising velocity of the P wave expresses that height of this wave which arises during 0 01 second supposing that velocity is constant Rising velocity means a combined function of the atrial myocardium its capacity to engender electrical potential and its conductivity Normally the rising velocity measures 0 286 mm per 0 01 second ± 0 111 which ranges from 0 10 to 0 75 mm per 0 01 second

In the present study the magnitudes of the angles of the atrial triangle were measured exactly The reliability of this procedure could be demonstrated by duplicate measurements In 50 cases a second measurement was performed at 20 to 30 days after the first determination The average difference between the two measurements amounted to ± 3 2° (−5° to 8°)

The angular configuration of the normal peaked P wave was as follows The ascending limb formed with the base line the angle α which had a magnitude of 44° ± 9 6 with a range from 20° to 77° The descending limb of the P wave returned to the base line determining the angle β which had an average magnitude of 51 5° ± 10 3 with a range from 22° to 73° The apex of the P wave was formed by the angle γ which had an average magnitude of 84 5° ± 19 7 with a range from 41 to 122° Consequently the normal peaked P wave was slightly asymmetrical because of the different magnitudes of angles α and β

The influence of cardiac rates on these fundamental elements of the P wave cannot be definitely settled The height of the P wave tends to increase with increasing cardiac rates The duration of the P wave *remains practically unaltered at different* cardiac rates Similarly Shipley and Hallaran [9] and Ashman and Hull were unable to demonstrate any relationship between heart rate and duration of the P wave The rising velocity shows a direct corre*lation with cardiac rates Its average at* low cardiac rates measured 0 201 mm per 0 01 second at medium cardiac rates 0 286 mm per 0 01 second and at high cardiac rates 0 295 mm per 0 01 second

The two basal angles of the atrial triangle tend to increase and the apical angle to decrease with increasing cardiac rates At low cardiac frequencies angle α presents its smallest values 41 9° and 39 5° At moderate and fast cardiac rates it increases exhibiting approximately identical values of 46 and 45° The behavior of angle β is similar The behavior of the apex angle is opposite to that of angles α and β

Age definitely influences myocardial func

tion and therefore the electrocardiogram Simonson[14] states that age is the most important biologic variable of the normal electrocardiogram and is responsible for a large number of false diagnoses in older people The present observations reveal that the height of the P wave decreases and its duration increases with advancing age

Rising time and rising velocity of the P wave are defined as functional manifestations of the atrial myocardium and are clearly influenced by age the rising time in the young age group averaged 0 0417 second (i e 45 7 per cent of the duration of the P wave) hence the projection of the peak of the atrial triangle fell to the right of its base deviated from the center by 4 3 per cent In the middle aged group rising time averaged 0 0469 second 49 4 per cent of the duration of the P wave so that in this group the peaked P wave was symmetrical the projection of its peak falling on the center of its base In *the group of aged subjects (over 51 years old)* the rising time was prolonged Its average measured 0 0595 second i e 60 9 per cent of the duration of the P wave The projection of the peak of the P wave was markedly deviated to the left (10 9 per cent from the center) Influence of age on the shape of the P wave can thus be summarized as follows the peaked P wave is symmetrical in middle aged subjects but asymmetrical with its peak deviated to the right in young subjects and to the left in older subjects

Rising velocity presents the same dependence on age as voltage or conduction In the subjects under 20 years of age rising velocity averaged 0 31 mm in the middle aged subjects it averaged 0 26 mm and in those over 51 years of age it decreased to an average of 0 20 mm per 0 01 second The progressive diminution of rising velocity of the normal P wave represents a hitherto undescribed manifestation of diminished functional capacity of the atrial muscle caused by aging

There is a close correlation between the angular structure of the P wave and age *The average magnitude of angle α in the youngest age group was 48* in the middle aged group it was 45° and in the old age group it exhibited its minimal magnitude of 41 9° The behavior of angle β was similar Angle γ representing the angular magnitude of the apex showed an opposite trend with increasing age Measured in the young age group its average was 82 5 in the middle aged group it was 83 2° and its maximal value of 86 9 was found in the old age group Consequently the angular elevation of the ascending limb of the peaked P wave decreases and the angular magnitude of the apex increases with age

Right atrial overactivity was studied in a group of 30 patients suffering from chronic pulmonary disease (emphysema chronic bronchitis bronchial asthma) The height of the P wave measured 2 31 mm ± 0 36 with a range from 1 6 to 3 0 mm (an average increase of 86 per cent) Sano and associates[7] found in similar cases P waves that were 2 3 mm in height Zuckerman and associates[illegible] in 50 cases of chronic cor pulmonale measured 1 9 mm (0 8 to 3 7 mm) and Oliveira and Zimmerman 2 7 mm (2 0 to 3 0 mm) Duration of the P wave averaged 0 096 second ± 0 014 identical with normal findings Rising time measured 0 05 second ± 0 013 (2 4 per cent shorter than the normal representing 51 7 per cent of the duration of the P wave)

Table III Correlation between normal peaked P wave and age (average values)

Age (yr)	Rate (min)	Height (mm)	Duration (sec)	Surface area (mm²)	Rising time		Fall time		Rising velocity (mm / 0 01 sec)	P R (sec)	V index	Angle		
					sec	%	sec	%				α	β	γ
<20	80 5	1 3	0 0838	5 58	041	45 7	044	54 3	0 31	0 149	1 36	48 7	48 8	82 5
21 50	80 3	1 26	0 0943	5 97	046	49 4	047	50 6	0 26	0 133	1 38	45 0	51 8	83 2
>51	79 5	1 22	0 0998	6 07	059	60 9	040	39 1	0 70	0 164	1 54	41 9	51 2	86 9

Table IV. Acute P pulmonale produced by breathing against manometric pressure

Number		Rate (min)	Height (mm)	Duration (sec)	Surface area (mm)	Rising time		Fall time		Rising velocity (mm/0.01 sec)	P-R (sec)	Macruz index	Angle		
						sec	%	sec	%				α	β	γ
1	Rest	75	1.6	0.12	9.6	Rounded		Rounded			0.20	1.50	43	61	76
	EE	107	4.0	0.08	16.0	05	63	03	37	0.80	0.14	1.33	78	76	26
2	Rest	1	1.0	0.10	5.0	Rounded					0.16	1.66	55	61	61
	EE	107	3.2	0.08	12.8	06	75	02	25	0.53	0.12	2.00	60	83	37
3	Rest	78	1.0	0.08	4.0	Rounded					0.18	0.80	42	70	68
	EE	125	2.4	0.10	12.0	08	80	02	20	0.30	0.14	2.50	46	75	59
4	Rest	83	1.4	0.11	7.7	Rounded					0.17	1.83	18	65	67
	EE	128	3.0	0.10	15.0	07	70	03	30	0.43	0.14	2.50	60	72	48
5	Rest	67	1.4	0.09	6.3	04	45	05	55	0.35	0.15	1.50	58	66	56
	EE	107	2.5	0.08	10.0	06	75	02	25	0.42	0.14	1.33	61	73	46
6	Rest	90	1.2	0.11	6.0	Rounded					0.15	2.75	38	53	89
	EE	120	2.2	0.10	11.0	06	60	04	40	0.37	0.14	2.50	58	62	60
7	Rest	83	1.0	0.11	5.5	06	55	05	45	0.17	0.15	2.75	45	45	90
	EE	125	2.0	0.10	10.0	06	60	04	40	0.33	0.14	2.50	61	62	57
8	Rest	68	2.0	0.10	10.0	Rounded					0.16	1.66	68	64	48
	EE	111	4.0	0.08	16.0	05	63	03	37	0.80	0.12	2.00	77	78	25
9	Rest	63	1.0	0.08	4.0	Rounded					0.15	1.14	56	73	51
	EE	82	2.0	0.08	8.0	05	63	03	37	0.40	0.12	2.00	65	75	40
10	Rest	62	1.2	0.09	5.4	04	45	05	55	0.30	0.16	1.29	55	57	68
	EE	104	2.0	0.08	8.0	05	63	03	37	0.40	0.15	1.14	60	69	51
11	Rest	66	0.8	0.10	4.0	Rounded					0.16	1.66	42	56	82
	EE	100	2.6	0.10	13.0	06	60	04	40	0.43	0.15	2.00	53	71	56
12	Rest	85	1.0	0.10	5.0	Rounded					0.14	2.50	45	58	77
	EE	125	1.5	0.08	6.0	06	75	02	25	0.25	0.12	2.00	38	76	66
13	Rest	69	1.2	0.09	5.4	04	45	05	55	0.30	0.16	1.29	40	52	88
	EE	107	3.0	0.08	12.0	05	63	03	37	0.60	0.12	2.00	62	73	45
14	Rest	69	1.4	0.09	6.3	04	45	05	55	0.35	0.16	1.29	50	58	72
	EE	96	3.5	0.08	14.0	05	63	03	37	0.70	0.12	2.00	74	76	30
15	Rest	71	1.2	0.10	6.0	06	60	04	40	0.20	0.16	1.66	35	60	85
	EE	97	3.0	0.08	12.0	05	63	03	37	0.60	0.12	2.00	49	68	63

EE: Expiratory effort.

According to the geometrical significance of the rising time the pulmonary P wave is traced almost symmetrically because projection of its peak deviates from the center to the left of the base line only by 1.7 per cent. The rising velocity was 0.475 mm. per 0.01 second ± 0.152 (0.17 to 0.77 mm. per 0.01 second) corresponding to an increase of 82 per cent.

The basal angles of the pulmonary P wave are wider than normal. Angle α measured 60.7° ± 8.7 (increased by 37.9 per cent) and angle β was 67.3° ± 6.0 (increased by 30 per cent). The angle γ of the apex was decreased (on an average 52.0° ± 11.5) indicating a diminution of 38.5 per cent.

Burger[12] in 1926 investigated the electrocardiographic changes that appear during expiratory effort (experiment of Valsalva) during breathing against manometric pressure. This author observed increased height of the P wave in every case. This method was employed to investigate the morphologic particularities of experimentally produced acute pulmonale P wave.

Breathing against manometric pressure produced the tallest of all the P waves examined. The average height was 2.73 mm., 120 per cent greater than our average normal standard, with ranges from 1.5 to 4.0 mm. The average duration measured 0.0966 second, the shortest, and the average surface area was 11.72 mm., the largest of all cases studied. Rising time averaged 0.0573 second, prolonged by 12 per cent as compared with the normal standard, representing 66.4 per cent of the duration of the

P wave Both figures indicate that the projection of the peak on the base of the atrial triangle is eccentric deviating from the center to the left by 16 4 per cent and that the trigonometric structure of the atrial triangle is most asymmetrical The average rising velocity was 0 49 mm per 0 01 second 104 per cent greater than in normal cases Measurement of the angular magnitude of this experimentally produced acute P pulmonale confirmed its skewness Angle α measured 60 1 and angle β 72 6° the average difference between the two basal angles was 12 5 60 per cent greater than in normal cases Angle γ was the most diminished measuring 47 3° i e 44 per cent less than the normal average The marked diminution of angle γ is apparent on simple inspection

The exact mechanism of production of the electrocardiographic pattern of pulmonary P is unknown Positional changes more vertically directed P vector increase of muscle mass with or without enlargement of the right auricular cavity and increased sympathetic nervous tone are frequently present Low oxygen saturation of the arterial blood plays a predominant role However in some cases the pulmonary P pattern can clearly be observed in the absence of any atrial abnormality (Mack and Snider[14])

Experiences with the Macruz index Macruz and associates[4] formulated simple quantitative criteria based on the conventional electrocardiogram for the recognition of right and left atrial enlargement According to these authors in normal conditions the duration of the P wave related to the duration of the P R segment is relatively constant presenting an average value of 1 2 with ranges from 1 0 to 1 6 In cases of right atrial enlargement the duration of the P wave remains unaltered but the P R interval increases so that the ratio of P to P R segment falls below the normal range On the other hand left atrial enlargement causes an increase in the duration of the P wave and a shortened P R segment and consequently the ratio of P to P R segment rises above the normal limit of 1 6 This simple test has been widely used in recent years and has been intensively investigated in the present study

Our experiences differed from those reported by Macruz and collaborators In 180 normal records the average ratio was 1 52 which figure agrees with that of the authors mentioned but the ranges were extremely wide varying from 0 7 to 5 0 Distribution was as follows less than 1 0 indicating right atrial enlargement was observed in 30 cases (16 7 per cent) normal values of 1 1 to 1 6 were present in 65 cases (36 1 per cent) and greater than normal values were observed indicating left atrial enlargement in 85 cases (47 2 per cent) Greater than normal ratios were observed in the following order 1 7 to 2 0 in 45 cases (25 0 per cent) 2 1 to 3 0 in 33 cases (18 3 per cent) 3 1 to 4 0 in 4 cases (2 2 per cent) and 4 1 to 5 0 in 3 cases (1 7 per cent) Consequently in perfectly healthy individuals the Macruz criteria are concordant with normalcy in 36 1 per cent only whereas they indicate abnormal conditions of the atria (sometimes very pronounced) in 63 9 per cent of these cases

Macruz and associates state that cardiac rates exert no significant effect on the magnitude of the ratio According to our experience the index of Macruz gives a maximum value of 1 79 slightly higher than the upper normal limit at medium cardiac frequencies of 71 90 whereas its average decreases at slower as much as at faster cardiac rates

In cases of chronic cor pulmonale the index of Macruz averaged 1 57 with ranges from 0 8 to 3 3 These figures are identical with those which we have observed in the group of normal subjects and thus the formulated ratio with its value of less than 1 0 was missed

In 15 cases transient acute right atrial overload was produced by breathing against manometric pressure In these cases and during rest the ratio was 1 56 (0 8 2 5) During forced respiration the ratio increased to 1 98 (+27 per cent) which is a paradoxical reaction This difference however is not statistically significant The standard error of the mean ratio in rest determined by the formula $\sqrt{\frac{\Sigma (\delta)}{n (n 1)}}$ was 0 147 and thus differences up to 3 S E M 0 441 are of no statistical significance The ratio increased during expiratory effort by 0 420 that is less

3 S.E.M., which is also not significant. In conclusion, we may state that the criteria evolved by Macruz and associates to indicate right or left atrial enlargement are diagnostically unreliable, first because normal variants are extraordinarily wide and secondly because changes in the ratio do not follow truly the observed functional and electrocardiographic alterations of the atria.

The quantitative study of the P wave as outlined in the present paper cannot unfortunately be used for changes of the P wave in the opposite direction, i.e., when its size decreases. Reduced magnitudes even of the normal P wave make it desirable to increase the sensitivity of the recording (in order to obtain greater deflections) and to increase the speed (in order to widen time intervals) as suggested by Abildskov.[3] Measurement of P waves with abnormally low deflections by means of the current method of recording is inaccurate and so unsuitable.

Summary

1. The P wave, specifically the peaked form variety, was studied in normal individuals, in subjects with cor pulmonale, and in those with acute experimental pulmonale P pattern produced by breathing against manometric pressure.

2. In addition to the conventional data, some new functional criteria, such as rising time and rising velocity, were investigated. The angular structure of the atrial triangle was examined and the standard values established.

3. The correlation between the linear and angular structure of the atrial wave and cardiac rate and age was established exactly.

4. The index of Macruz was critically examined in light of the conditions described, and its diagnostic value assessed.

5. The methods of investigation herein described increase the diagnostic value of the conventional electrocardiogram with respect to the atrial wave.

Addendum

Since the preparation of this paper Kahn and associates[15] have published a report in which they conclude that the ratio of Macruz is not a reliable test of atrial enlargement.

REFERENCES

1. Langner, P. H., Jr.: The value of high fidelity electrocardiography using the cathode ray oscillograph and an expanded time scale, Circulation 5:249, 1952.
2. Hellerstein, H. K., Shaw, D., and Sano, T.: Dissection of the vectorcardiogram: differential vectorcardiography, AM. HEART J. 47:887, 1954.
3. Abildskov, J. A.: A quantitative study of the electrocardiographic effects of atrial enlargement, AM. HEART J. 53:55, 1957.
4. Macruz, R., Perloff, J. K., and Case, R. B.: A method for the electrocardiographic recognition of atrial enlargement, Circulation 18:887, 1958.
5. Gross, D.: A single numerical correlation between the quotient Q-T/T-Q and cardiac rate in healthy adults, Am. J. Physiol. 170:121, 1952.
6. Ashman, R., and Hull, E.: Essentials of electrocardiography, New York, 1941, The Macmillan Company, p. 260.
7. Sano, T., Hellerstein, H. K., and Vayda, E.: P vector loop in health and disease as studied by the technique of electrical dissection of the vectorcardiogram, AM. HEART J. 53:854, 1957.
8. Stewart, C. B., and Manning, G. W.: A detailed analysis of the electrocardiogram of 500 R.C.A.F. aircrew, AM. HEART J. 27:502, 1944.
9. Shipley, R. A., and Hallaran, W. R.: The four-lead electrocardiogram in 200 normal men and women, AM. HEART J. 11:325, 1936.
10. Simonson, E.: The normal variability of the electrocardiogram as a basis for differentiation between normal and abnormal, AM. HEART J. 55:80, 1958.
11. Zuckerman, R., Cabrera, E., Fishleder, B. L., and Sodi-Pallares, D.: Electrocardiogram in chronic cor pulmonale, AM. HEART J. 35:421, 1948.
12. Oliveira, J. M., and Zimmerman, H. A.: Auricular overloadings, Am. J. Cardiol. 3:453, 1959.
13. Bürger, M.: Die Herzstromkurve unter der Einwirkung intrapulmonaler Drucksteigerung, Ztschr. ges. exper. Med. 52:231, 1926.
14. Mack, I., and Snider, G. L.: Respiratory insufficiency and chronic cor pulmonale, Circulation 13:419, 1956.
15. Kahn, M., Scheuer, L., Wachtel, F., Grishman, A., and Donoso, E.: An evaluation of the ratio of P wave duration to P-R segment in the diagnosis of atrial enlargement, AM. HEART J. 60:23, 1960.

Kinetocardiographic findings in patients with congestive heart failure and changes after therapeutic digitalization

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Recent work done in this laboratory described alterations in precordial movements during anginal attacks and the effect of therapeutic doses of glyceryl trinitrate on these abnormal deflections These observations have been confirmed and evidence introduced that transient failure occurs at the time of anginal pain in some patients a finding noted previously by Muller and Rorvik[3] during right heart catheterization

The purpose of this communication is to report abnormalities in tracings of precordial motions in patients with evidence of congestive heart failure the changes produced by therapeutic digitalization and in a few instances digitalis intoxication

Methods

Low frequency precordial movements (kinetocardiograms KCG) were recorded by the bellows crossbar technique as previously described The same terminology is used as before i e K_1 represents tracings recorded from the right parasternal line (V) K from the vertical line corresponding to the V lead of the ECG etc A second numeral in the subscript indicates the intercostal space from which the record was taken i e a K_{15} tracing is one from the right parasternal line in the fifth intercostal space

The K through the K_4 areas were studied however findings from the K and K positions were the most striking and consistent and are the ones reported The areas studied were marked on each patient with an indelible solution to aid in reproducible placement of the bellows with successive tracings

Five movements are considered (Fig 1) Those recorded after atrial excitation and before ventricular excitation are due to atrial activity and two have been chosen for study an initial outward deflection termed the atrial upstroke (AU) and a second inward motion referred to as the atrial downstroke (AD) When no distinct separation of passive ventricular filling (VF) and atrial upstroke deflections occurred the AU value could not be determined

The major inward (downward) deflections recorded at the K area after the onset of Q of the ECG is attributed to change of volume as the ventricles eject[4] This motion is constantly present in normal subjects and is the largest deflection associated with ventricular systole at this area it will be referred to as the ventricular ejection downstroke (EDS)

A mid systolic outward movement (MOM) and a motion previously attributed to passive ventricular filling (VF) are reported

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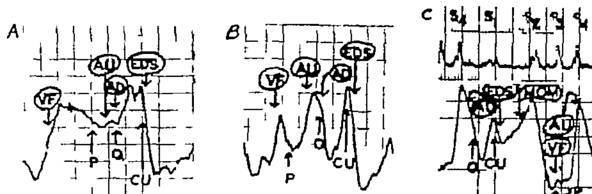


Fig 1 Paper speed 50 mm/sec Tracings begin and end in diastole so as to better demonstrate changes in passive filling and atrial contraction The characteristic movements in a normal subject (A) a patient with predominant left ventricular failure (B) and a patient with biventricular failure (C) are shown A Note the small atrial upstroke movement (AU) occurring after the P wave of the ECG and the ventricular ejection downstroke motion (EDS) which occupies a major portion of the total amplitude of the complex The ventricular filling wave (VF) is quite prominent B The atrial upstroke motion (AU) is markedly increased and the passive ventricular filling wave (VF) decreased The ventricular ejection downstroke (EDS) continues to constitute a major portion of the total amplitude of the entire complex C The atrial upstroke motion occupies a major portion of the total amplitude of the entire complex The ventricular ejection downstroke (EDS) is markedly decreased and the ventricular filling wave is quite small A mid systolic outward movement (MOM) is now present Note the absence of this latter movement in records A and B A definite separation of ventricular filling and atrial upstroke motions exists The rectified heart sound recordings demonstrate both a protodiastolic gallop (S) and an atrial gallop (S) the former is correlated with the tiny ventricular filling wave (VF) and the latter with the prominent atrial upstroke motion (AU) AD Atrial downstroke TA Total amplitude P P wave of ECG Q Q wave of ECG CU Carotid upstroke VF Passive ventricular filling All sounds rectified S S S S First second and third heart sounds and fourth (atrial) sound respectively

To determine more accurately the serial changes in the kinetocardiograms as treatment for congestive failure progressed the amplitudes of the atrial and ventricular movements were expressed as a percentage of total amplitude of the complete cardiac cycle complex Total amplitude (TA) was determined by measuring the distance from the highest to the lowest point of a given cardiac cycle (Fig 1) Five percentages were calculated indicating the following relationships AU/TA × 100 AD/TA × 100 EDS/TA × 100 AU/EDS × 100 and AD/EDS × 100

Patients

Before the study of patients with congestive heart failure was undertaken the effects of digitalis on the KCG of 6 normal persons were first determined Fourteen patients were then studied Six had clinical evidence of predominant left ventricular failure and 8 displayed biventricular failure Table I shows the clinical and objective evidence for cardiac decompensation in each Twelve had never received any form of treatment for failure prior to the study 2 had received both diuretics and digitalis in the past but were essentially undigitalized since marked improvement followed large doses of the drug Serial records were obtained on each during the digitalizing process

Results

Fig 2 illustrates the reproducibility of the records and shows four consecutive daily tracings from the K area taken at the same sensitivity from a normal man No significant variability occurred from day to day in relative amplitudes of atrial or ventricular motions

The 6 normal subjects exhibited no significant change in the KCG after digitalization (Fig 3)

Atrial movements Previous studies[7] in normal subjects of various ages have shown that the atrial upstroke movement does not exceed 27 per cent of total amplitude In a series of normal subjects who were over 35 years of age the mean percentage atrial downstroke (AD) of total complex excursion was 21 with only one value in excess of 27

Table II shows values for the two atrial movements before and after digitalization

No untreated patient had an AU/TA value of less than 37 per cent (mean 47 per cent) or an AD/TA percentage of less than 20 per cent (mean 38 per cent) The means after maximum doses of digitalis were 18 5 and 18 1 per cent respectively Each subject showed a decrease in these relative percentages as treatment progressed (Figs 7 and 8)

The atrial downstroke percentage (AD/TA × 100) showed a wide scatter (Fig 4) before treatment 5 patients 4 of whom were suffering from biventricular failure had high percentages After therapy values were within upper limits of those established for normal

Ventricular ejection downstroke The range for this movement at the K area was wide in both normal subjects and patients with untreated failure (Fig 4) Those with predominant left ventricular failure had essentially the same means before and after digitalization (7 and 87 per cent respectively) whereas all with biventricular failure had values below 30 per cent one showed a value below 30 per cent after digitalization

Ratio of atrial movements to ventricular ejection downstroke The AU EDS ratio ranged from 48 to 1 400 per cent (median 87 per cent) before treatment and 17 to 58 per cent after digitalization Those with biventricular failure had values in excess of 100 per cent (146 to 1 400 per cent) whereas those with primarily left ventricular failure showed a range of 48 to 87 per cent The two highest values after therapy 45 and 58 per cent were from

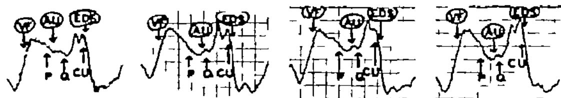


Fig 2 This figure shows the reproducibility of records obtained from a normal 24 year-old man over four consecutive days from one area the left parasternal line in the fifth intercostal space (K) Each tracing begins and ends with the carotid incisural notch and represents one complete cardiac cycle Time lines are 0 0 second The recording apparatus was calibrated before each tracing was made in order to assure the same sensitivity for each tracing obtained The subject was marked with an indelible solution to aid application of the bellows at the same point each time Note the reproducibility seen in both configuration and amplitude No appreciable variation in atrial movements or ventricular ejection movements is seen *P* P of ECG *Q* Q wave of ECG *CU* Carotid upstroke *AU* Atrial upstroke *EDS* Ventricular ejection downstroke *VF* Passive ventricular filling wave

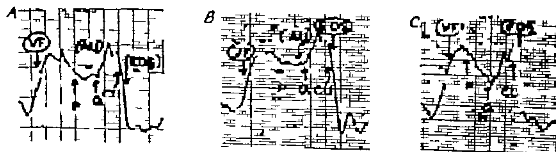


Fig 3 This figure shows the effect of digitalis on kinetocardiograms taken from a normal subject All records begin and end with the carotid incisural notch and are from the left parasternal line fifth intercostal space (K) Time lines are 0 0 second *A* Control record *B* After 10 mg of gitalin (mg /day for 5 days) *C* Eight days after withdrawal of digitalis The control record the tracing taken after ingestion of 10 mg of gitalin and the recording made 8 days after withdrawal of the drug show no essential differences Clinically the only effect noticed was a varying degree of malaise When this figure is compared to Fig 8 the marked effect of digitalis on the failing heart as reflected by the KCG is clearly seen *P* P wave of ECG *Q* Q wave of ECG *CU* Carotid upstroke *AU* Atrial upstroke *EDS* Ventricular ejection downstroke *VF* Passive ventricular filling

Table I. Summary of data on patients studied

Patient	Sex	Age (yr)	Type of congestive heart failure*	Diagnosis	Dyspnea: Effort	Dyspnea: Rest	Edema	Orthopnea	PND†	Circulation time‡ (sec)	Vital capacity (L): Before digitalization	Vital capacity (L): After digitalization	Loss of weight after digitalization (lb)	Digitalis preparation used	Diuretics used
1 Q I	F	59	BVF	HCVD CAD	Yes	N	Minimal	No	N	31	2.0	2.8	9	Gitalin	No
2 H A	M	59	BVF	HCVD	Yes	Yes	Anasarca	Yes	Yes	58	2.0	3.2	25	Gitalin	N
3 M S T	F	53	BVF	CAD	Yes	Yes	Moderate with hydrothorax	Yes	Yes	24	1.0	1.8	16	Gitalin	N
4 O D	F	67	BVF	AI	Yes	Yes	Anasarca	Yes	Yes	—	1.0	—	89	Digoxin	Yes
5 W H	M	48	BVF	AI	Yes	Yes	Moderate with hydrothorax	Yes	Yes	29	1.0	2.2	16	Gitalin	N
6 J M	M	26	BVF	AI	Yes	Yes	Moderate with ascites	Yes	Yes	36	2.8	3.4	4	Gitalin	No
7 J W	M	60	BVF	AI	Yes	Yes	Moderate	Yes	Yes	28	2.0	3.8	9	Gitalin	Yes
8 L S	M	62	LVF	CAD	Yes	N	No	N	—	23	3.8	3.8	0	Gitalin	No
9 W M	M	58	LVF	CAD	Yes	Yes	No	No	Yes	—	4.5	—	0	Gitalin	N
10 H W	M	55	LVF	CAD	Yes	N	N	N	Yes	—	4.5	—	0	Gitalin	N
11 W N	F	70	LVF	CAD	Yes	No	N	Yes	Yes	—	1.6	2.2	0	Gitalin	N
12 W K	M	[illegible]1	LVF	AI	Yes	Yes	No	Yes	Yes	—	1.2	2.8	0	Gitalin	No
13 L P	M	64	LVF	AI	No	Yes	No	N	Yes	—	1.8	2.8	5	Gitalin	No

*BVF, Biventricular failure; LVF, Left ventricular failure only.
†PND, Paroxysmal nocturnal dyspnea.
‡Arm-to-tongue circulation time.
HCVD, Hypertensive cardiovascular disease.
CAD, Coronary artery disease; AI, Aortic insufficiency.

Table II. Percentage of the parameters studied in patients with congestive heart failure before and after digitalization

Patient	AU/T1 × 100		AD/T1 × 100		ADV/T1 × 100		AL/LDS × 100		AD/LDS × 100		Type of cardiac failure
	Before digitalization	After digitalization	Before digitalization	After digitalization	Before digitalization	After digitalization	Before digitalization	After digitalization	Before digitalization	After digitalization	
1 Q F	47	20	43	25	79	90	150*	2	90	33	B
2 W H	40	15		—	3	61	1 400	25		—	B
3 M S [illegible]			60	27	0	17	—	—	175	60	B
4 O D	43	15	76	5	29	43	146	33	175	20	B
5 H A		—	55	1	10	71			1 100	17	B
6 J M	45	2	62	27	27	37	167	38	186	29	B
7 J W	75	14	25	27	43	31	167	45	50	86	B
8 L W S	37	6	79	10	56	90	65	29	70	4	I
9 W M	53	20	20	17†	100	91	53	2	28	17†	L
10 W N	13	16	27	1	50	81	57	19	35	21	I
11 H W	42	14	45	2	55	81	48	17	56	31	I
12 I I	55	7		—	93	100	59	7	—	—	I
13 W K	40	14	23	6	74	79	54	17	31	10	I

[illegible]

Table III. Effect of digitalis intoxication on kinetocardiograms

Patient	AU/T1 × 100			AD/T1 × 100			ADS/T1 × 100			AL/LDS × 100			AD/LDS × 100		
	Before digitalization	After digitalization	Digitalis intoxication	Before digitalization	After digitalization	Digitalis intoxication	Before digitalization	After digitalization	Digitalis intoxication	Before digitalization	After digitalization	Digitalis intoxication	Before digitalization	After digitalization	Digitalis intoxication
W K	40	15	50	25	17	51	74	9	65	54	17	77	35	22	82
L W S	54	28	44	20	22	41	42	91	71	130	31	60	0	24	58
M S T	—	—	—	97	34	34	0	17	3	—	—	—	400	700	1 200

[illegible]

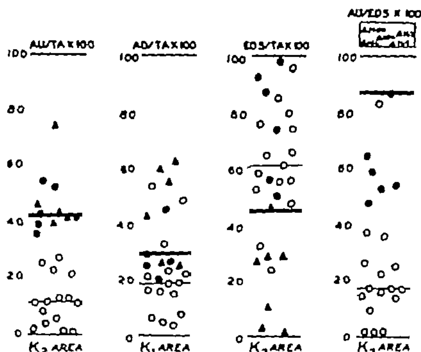


Fig 4 This figure shows comparison of the various parameters studied in normal subjects and in patients with untreated cardiac failure Left to right A D A Atrial upstroke motion A clear separation of normal subjects and patients with failure occurs The median for the normal subjects 12 per cent and the median for the untreated patient with cardiac failure is 44 per cent B Atrial downstroke motion The difference in medians between the normal subjects and patients with untreated failure is apparent however considerable degree of overlap exists as regards distribution of values C Ventricular ejection downstroke motion Little overlapping occurs with the two types of patients studied The 5 patients who show values below 30 per cent were those with biventricular failure and the 6 with values of 50 per cent or greater had clinical evidence of left ventricular failure only Three of the 16 normal subjects exhibited values below 50 per cent with only one below 40 per cent D Ratio of atrial upstroke amplitude to ventricular ejection down stroke amplitude Very little overlap occurs the difference in medians is quite marked Five of the untreated patients had values above 100 per cent only one normal subject had value in excess of 37 per cent White circles Normal subject Black circles Untreated patients with predominant left ventricular failure Black triangles Untreated patients with biventricular failure Double horizontal rules Median for all patients Single horizontal rules Median for normal subjects AU Atrial upstroke AD Atrial downstroke EDS Ejection downstroke (ventricular) TA Total amplitude

subjects with long standing biventricular failure

The range of the AD EDS percentage in untreated patients was 28 to 100 per cent after therapeutic digitalization it was 10 to 86 per cent and two values were above 33 per cent

The changes noted in each patient before and after digitalization are presented in Table II and Figs 5 and 6

Ventricular mid systolic movement An exaggerated mid systolic movement was present at the K2 area in all patients with untreated biventricular failure The effect of digitalis on this is shown in Fig 8 After maximal digitalization this motion disappeared in 4 of 7 subjects markedly decreased in 2 and failed to show any change in 1

Changes in serial kinetocardiograms All patients showed a progressive decrease in atrial motions while being digitalized Fig demonstrates the results obtained over 5 consecutive days from the untreated state to full digitalization in a patient suffering from failure of both ventricles This was representative of all patients and was correlated with more classic objective evidence of improvement (decreased severity of symptoms increased vital capacity decreased circulation time etc)

The actual complexes from which data for Fig 7 were derived are shown in Fig 8 A marked reduction in atrial deflections was seen 18 hours after oral digitalis therapy was begun a time at which minimal increase in the ventricular ejection downstroke occurred When the latter movement did show early accentuation it was only in those patients with failure of short duration

In the tracing shown in Fig 8 the mid systolic outward movement progressively decreased as digitalization became complete and disappeared entirely 3 days after the drug was started

Every patient showed an increase in the amplitude of the passive ventricular filling wave as treatment with digitalis progressed this was concomitant with the decrease in atrial deflections

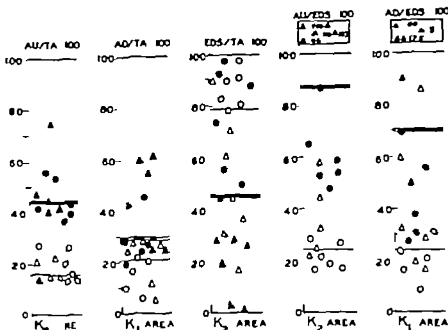


Fig This figure shows percentage values for the 5 parameters studied before and after therapeutic digitalization Left to right *A* AU Atrial upstroke motion The median for this movement fell from 44 per cent (range 37 to 75 per cent) before digitalis therapy to 17 per cent after full digitalization (range 14 to 27 per cent) *B* Atrial downstroke motion This ranged from 20 to 6 per cent (median 28 per cent) before digitalization and 5 to 7 per cent (median 22 per cent) after digitalization All showed decrease in relative amplitude of this movement after therapy *C* Ventricular ejection downstroke motion The medians before and after digitalization are 4 (range 0 to 100) and 79 per cent (range 17 to 100 per cent) respectively Five patients all with biventricular failure had values below 80 per cent before digitalization and only one had less than 30 per cent after maximum doses of the drug this one being studied after long standing severe biventricular failure The scatter here is so marked that no significance can be attached to this determination as regards the group of patients studied however changes in individual patients indicated a trend toward significant increases after digitalization especially in the patients with biventricular failure *D* Comparison of atrial upstroke amplitude to ventricular ejection downstroke amplitude This ranges from 48 to 1 400 per cent (median 83 per cent) before therapy was begun and 17 to 58 per cent (median 25 per cent) after full digitalization The values over 100 per cent observed before treatment were seen only in those patients with clinical evidence of biventricular failure Only 2 patients had values in excess of 35 per cent after digitalization and both had been in biventricular failure of long duration *E* Atrial downstroke amplitude to ventricular ejection downstroke amplitude The predigitalization median for this parameter was 70 per cent (range 78 to 1 100 per cent) and the post-digitalization median was 24 per cent (range 10 to 86 per cent) The highest values recorded after maximal drug dosage were from those with prolonged and severe biventricular failure Black triangles Untreated patients with biventricular failure (BVF) before digitalization White triangles After digitalization (BVF) Black circles Untreated patients with left ventricular failure (LVF) before digitalization White circles After digitalization (LVF) Double horizontal rules Median before digitalization Single horizontal rules Median after digitalization *AU* Atrial upstroke *EDS* Ventricular ejection downstroke *AD* Atrial downstroke *TA* Total amplitude

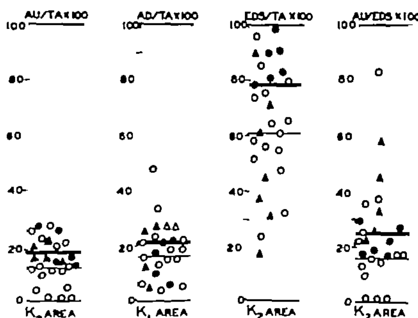


Fig 6 This figure shows a comparison of normal subjects and fully digitalized patients who have improved from congestive heart failure Left to right *A* *D* *A* Atrial upstroke motion The median for both normal subjects and digitalized improved patients with failure is approximately the same the range for the treated patients falls within that for normal subjects *B* Atrial downstroke motion Again values for both normal subjects and fully digitalized patients are almost identical *C* Ventricular ejection downstroke The scatter is so marked that no significance can be attached to it the range however is almost identical for both groups *D* Atrial upstroke amplitude to ejection downstroke amplitude Medians for the two types of subjects are almost identical All treated patients with failure fall within the range for normal subjects Fully digitalized patients improved from heart failure black triangles = biventricular failure black circles = predominant left ventricular failure only White circles = normal subjects Double horizontal rules Median for patients Single horizontal rules Median for normal subjects *AU* Atrial upstroke *AD* Atrial downstroke *EDS* Ventricular ejection downstroke *TA* Total amplitude

Effect of intravenous digitalis on the kinetocardiogram One patient who was taking oral digitalis but was underdigitalized and had obvious biventricular failure was given a total of 0.4 mg of lanatoside C intravenously after a series of control records were obtained In 2 hours a decrease in the atrial upstroke increase in ejection downstroke and decrease in percentage AU/EDS were observed (Fig 9) An increase in the passive ventricular filling wave was also noted These changes were similar to those produced by slow oral digitalization

The kinetocardiographic changes with clinical evidence of digitalis intoxication Of 9 patients with digitalis intoxication 6 had gastrointestinal manifestations only and these for a brief period These patients exhibited no changes due to excessive amounts of the drug from records taken shortly before However 3 had evidence of severe intoxication of several hours duration and 2 showed cardiac changes (ECG increased severity of failure) These 3 displayed kinetocardiographic changes comparable to those obtained during the untreated state Table III shows the parameters studied before treatment at the time of maximal digitalis response and after ingestion of excessive amounts of the drug Fig 10 shows complexes at various levels of management

Discussion

All patients with heart failure exhibited alterations in ventricular filling manifested by reduced passive ventricular filling waves and exaggerated movements associated with atrial contraction Patients with biventricular failure displayed two additional changes which were not present in patients with left ventricular failure alone These changes

were decreased inward motions associated with rapid ventricular ejection and increased mid systolic outward deflections.

The decreased passive ventricular filling waves and increased atrial movements are presumably the result of a decrease in ventricular contractility leading to defective emptying, increase in residual volume, increase in ventricular diastolic pressure, and usually a decrease in stroke volume.[19] This leads to distention of the ventricle and thus atrial distention. Consequently the atrium contracts with more vigor and an increase in amplitude of recorded atrial movements occurs. Ventricular filling is thus accomplished more by atrial contraction and less by passive inflow since rapid equalization of pressures between the atrium and ventricle occurs with the latter. Therefore the passive ventricular filling wave as recorded by the kinetocardiogram is reduced in amplitude.

These findings as regards *atrial motions* are in agreement with those of Dock.[22] The discrepancy of this work with that of Dock and Heyer[23] as related to the *passive ventricular filling wave* is more apparent than real. Heyer, using the electrokymogram, found the duration of passive filling to be shorter in patients with congestive heart failure and Dock, using the ballistocardiogram, found large protodiastolic movements in such patients. The former work points toward rapid equalization of pressures between atrium and ventricle by small volumes of blood entering an already distended ventricle; the latter work points toward increased force of blood moving into the ventricles during early diastole. Thus it would appear that during congestive failure the force of early filling is augmented even though the volume is diminished.

When patients with left-sided failure only were compared with those who had defective action of both ventricles, certain similarities and certain differences were noted. Both groups exhibited exaggerated atrial and decreased passive filling motions. However, the ejection downstroke, which is probably related to the output during rapid emptying, was different in the two groups, being essentially normal when only the left ventricle was at fault but sharply decreased when right ventricular failure was also present. The explanation for this observation is possibly related to the differences in the architecture and pressure-volume relationships of the two chambers. In the thick-walled left ventricle a small rise in diastolic volume will lead to a large increase in pressure and hence to pulmonary congestion. However, the signs of right-sided failure, being related to a rise in pressure in this more distensible chamber, will occur only after a relatively large amount of residual blood has accumulated. Thus the congestive manifestations occur early in relation to the degree of dilatation in the case of the left ventricle and at a time when this chamber is still able to maintain a relatively normal resting output. The reverse is true of the right ventricle.

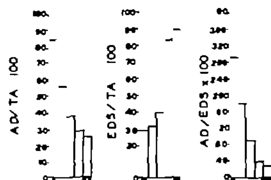


Fig. 7. Results of records obtained on Patient Q. F. over 5 consecutive days from control to full digitalization. All determinations are from the K region. This figure shows graphically the changes noted in tracings of Fig. 8. Left to right: A, C, A. Daily changes in percentage atrial downstroke (AD) amplitude of total complex amplitude (TA) over 5 days of digitalization with oral gitalin. A precipitous decrease in this percentage occurred 24 hours after initiation of therapy. An essentially stepwise decrease in this movement occurs with progressive digitalization. B, Changes in the percentage of total amplitude occupied by the ventricular ejection downstroke amplitude with progressive digitalization. Unlike the atrial upstroke and downstroke, dramatic response in this parameter did not occur until the fourth day of digitalization (see text for explanation). C, The daily effect of digitalis on the percentage atrial downstroke of ejection downstroke amplitude (AD/EDS × 100). Again a stepwise decrease occurs with an early marked fall. This relative movement decreased from 85 to 28 per cent. Record obtained before initiation of digitalis therapy. Record obtained after full digitalization. AD, Atrial downstroke amplitude. TA, Total amplitude of complex. EDS, Ventricular ejection downstroke amplitude.

The mid systolic outward movement (Figs 1 and 8) present in records obtained from patients with untreated biventricular failure resembles that of patients with right ventricular hypertrophy[14] and is also similar to the bulge seen in patients at the time of anginal pain and in some patients after myocardial infarction. The cause for this is unknown at present.

The mechanisms by which the passive ventricular filling wave increases and the atrial deflections decrease after digitalization are presumably explained as follows: Augmented myocardial contractility is one of the major effects of digitalis.[1-4] This causes more complete emptying, decrease in residual volume,[15, 4-44] reduced ventricular diastolic pressure and usually an increase in stroke volume.[17, 4-44] Under these conditions the now less distended ventricle can fill more before pressure equalization with the atrium occurs. Ventricular filling is accomplished to a greater extent by passive rapid filling (Fig 9) and less by atrial contraction because the less distended atrium contracts less vigorously.

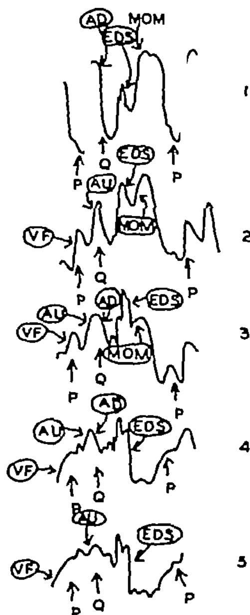


Fig 8 (Legend opposite)

Fig 8 Shows the daily changes in kinetocardiograms of Patient Q F obtained over 5 consecutive days from control to full digitalization from area K. *1* Control record. No digitalis. This record shows the difficulty in interpreting large outward (upward) movements that occur after atrial excitation when not preceded by a definite ventricular filling wave. It is impossible under such circumstances to state how much of this movement is actually due to atrial activity since both atrial systole and passive ventricular filling may be responsible for its production (see text). The atrial downstroke (*AD*) however is markedly exaggerated (compare with normal tracing Fig 1). A small ventricular ejection downstroke (*EDS*) and large mid systolic outward movement (*MOM* bulge) are seen. Twenty four hours after initiation of digitalis therapy (3 mg gitalin) four striking changes have occurred: (a) the appearance of a definite passive ventricular filling wave (*VF*) and atrial upstroke (*AU*); (b) marked decrease in the atrial downstroke (*AD*); (c) a slight increase in the ventricular ejection downstroke; and (d) significant reduction in the mid-systolic bulge (*MOM*). *3* Forty-eight hours after digitalization (5 mg gitalin) was begun the same changes as noted in tracing *2* above have occurred but are slightly greater in degree, the most prominent being the increased *EDS* and decreased *MOM*. *4* Seventy two hours after beginning digitalization (7 mg gitalin) a marked decrease in the atrial movement has occurred with a concomitant increase in the ventricular filling wave (*VF*). The ventricular ejection downstroke now occupies a large percentage of total amplitude and the bulge has eventually disappeared. *5* At the time of full digitalization (9 mg gitalin) the most striking changes are continued increase in the passive ventricular filling movement and continued decrease in the recorded atrial deflection. Note: The heart rate at the time record *5* was taken was the same as that at the time tracing *1* was recorded. *P* P wave of ECG. *Q* Q wave of ECG.

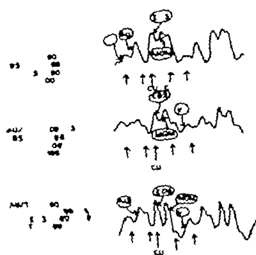


Fig 9 This figure illustrates the effect of intra enous lanatoside C on kinetocardiograms obtained from a patient ith marked decompensation (bi entricu lar failure) ho had been on maintenance digitalis therapy All records were taken f om K_4 *A* Control record The trial upstroke (*A U*) motion is clearly defined as separate entity constituting 43 per cent of total amplitude The entricular ejection downstroke (*EDS*) is markedl decreas ed (see normal record Fig 1) and prominent sustained bulge (mid systolic outward movement *MOU*) is readily isualized *B* One hour after 0 2 mg of lanatoside C intra enously The trial upstroke (*A U*) deflection has become less prominent the entricular ejection downstroke (*EDS*) has doubled in amplitude and the mid systolic outward mo ment (bulge *MOU*) is shorter in duration being much less sustained than in the control record The entricular filling a has become slightly more prominent *C* T hours after first 0 2 mg intra enous dose of lanatoside C and one hour after second 0 2 mg intravenous dose The trial mo ment (*A U*) remains below the control alues but shows no marked decrease The ejection downstroke has increased considerably being pproximately three times greater than the control value similarly the mid systolic outward movement is much less sustained The entricular filling wa (*V F*) has shown an increase Note The patient heart rate remained at 70 beats per minute throughout the entire procedure and each record was taken from the same point on the precordium *P* P of ECG *Q* Q ve of ECG *CL* Carotid upstroke *CIN* Carotid inci ural notch

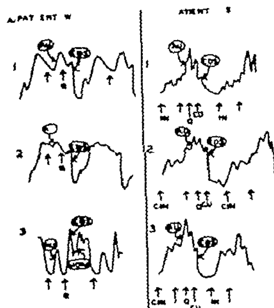


Fig 10 This figure show the kinetocardiographic changes noted t the time of u treated congesti failure full compensation th therapeutic doses of digitalis and t the time of digitalis intoxication i patients one th moder te nd one with severe ntoxication *A* Record from K area *I* Mild untreated left entricular failure Note the promi nent but not markedly accentuated tri l upstroke motion (*A U*) and the essentially normal entricular ejection dow troke (*EDS*) movement *2* Full compensation The trial p troke deflection is markedly reduced and the entricular jection downstroke remains quite normal *3* Severe di italis intoxication The trial movements are now quite conspicuous nd accentuated the jection down stroke is markedly reduced (compare th *I* abov) and bulge (mid systolic outward movement *MOU*) has appeared KCG criteria (see text) for biventricular failure are met in th record nd absent in the first tw record indicating more severe degree of failure ith digitalis intoxication than existed initially *B* Records from K area *I* Mild ntreated left entricular failure A prom nent atrial pstroke (*A U*) is present the entricular ejection downstroke (*EDS*) reduced t below 50 per cent of total amplitude *2* F ll compensation The trial upst oke deflection is approximatel one half of that seen in the record obta ned before therapy was begun and the ejection downstroke now contributes to 90 per cent of total amplitude *3* Moderate digitalis ntoxication Th trial up stroke is now pproximately the same as that seen in the initial record (*B I*) the entricular ejection downstroke is reduced but does not pproach that seen in the control record Abbreviations *CL* Carotid up troke *CIN* Carotid incisural notch *P* P of ECG *Q* Q wa of ECG

Consequently a reduction in recorded amplitude of atrial movement occurs[11] Fig 7 shows that the decline in atrial motions preceded the increase in the ventricular ejection downstroke This is interpreted to indicate that a slight reduction in ventricular residual volume and pressure causes a marked decrease in the distention of the thin walled atrium Thus the force of the atrial contraction and atrial deflections as recorded by the KCG decreases as improvement occurs This is in keeping with the work of Stead and associates[6] who found a fall in atrial pressure to be the first change noted after the intravenous administration of digitalis

With progressive digitalization patients with severe cardiac failure of long duration demonstrated slower changes in atrial movements than did those with moderate decompensation It is likely that digitalis in the former patients was not capable of producing full compensation because of less reversibility of the prolonged untreated state This is consistent with the findings of Ferrer and associates[7] who showed that pulmonary arterial pressures fell to normal limits shortly after intravenous digitalis was administered in those patients with mild to moderate failure longer time was required for this same effect in those more incapacitated

It has been reported[8,?] that patients develop an increase in the severity of congestive failure with digitalis intoxication Objective evidence for this is shown through the KCG The similarity of records obtained from patients at the time of digitalis intoxication and when untreated is marked

Summary

Kinetocardiographic alterations before and after digitalis therapy in patients with congestive heart failure are presented The most consistent finding during failure was an increase in the atrial movements which decreased to normal levels after maximal doses of digitalis Inconsistent alterations in ventricular ejection movements were noted

Patients in failure had decreased passive ventricular filling waves which increased after digitalization A possible explanation for this is presented

Digitalis intoxication produced changes in kinetocardiograms that resembled those seen in untreated patients with failure thus offering objective evidence that an excess of this drug will cause an increase in failure

REFERENCES

1 Harrison T R and Hughes L Precordial systolic bulges during anginal attacks Tr A Am Physicians 71 174 1958
2 Skinner N S Jr Leibeskind R S Phillips H L and Harrison T R Angina pectoris effect of exertion and of nitrites on precordial movements Am Heart J 61:250 1961
3 Muller O and Rorvik K Hemodynamic consequences of coronary heart disease with observations during anginal pain and on the effect of nitroglycerin Brit Heart J 20:302 1958
4 Eddleman E E Jr Willis K Reeves T J and Harrison T R The kinetocardiogram I Method of recording precordial movement Circulation 8:269 1953
5 Harrison T R Lowder J A Hefner L L and Harrison D C Movements and forces of the human heart V Precordial movements in relation to atrial contraction Circulation 18:8? 1958
6 Norman J R and Harrison T P Movements and forces of the human heart IV Precordial movements (kinetocardiograms) relation to ejection and filling of the ventricle A M A Arch Int Med 101:58? 1958
7 Ingram R H Kinetocardiographic findings normal subjects after standard exercise procedure Thesis presented to the faculty of Yale University School of Medicine 1960
8 Starling E H Linacre Lecture on the Law of the Heart Cambridge 1915 New York 1918 Longmans Green and Co
9 Sarnoff S J Myocardial contractility as described by ventricular function curves observations on Starling law of the heart Physiol Rev 35 107 1955
10 Seymour W B Pritchard W H Longley L P and Hayman J M Jr Cardiac output blood and interstitial fluid volumes total circulating serum protein and kidney function during cardiac failure and after improvement J Clin Invest 21 229 1942
11 Cournand A A discussion of the concept of cardiac failure in the light of recent physiological studies in man Ann Int Med 37:649 1952
12 Dock W The three plane ballistocardiogram in heart failure Am J Cardiol 3:384 1959
13 Heyer H E Howard C H Willis K W and Pickle A C Alterations in the rapid filling phase in congestive heart failure Am Heart J 43 206 1952
14 Eddleman E E Jr and Thomas H D The diagnosis of right ventricular hypertrophy Am J Cardiol 4:652 1959
15 Kyu S and Eddleman E E J Kinetocardiographic findings of myocardial infarction Circulation 19 531 1959

16 Stead E A J Warren J V and Brannon E S Effect of lanatoside C on the circulation of patients with congestive failure Arch Int Med 81 78 1948
17 Richards D W J Cournand A Darling R C Gillespie W H Baldwin E DeF Pressure of blood right uncle in animals and in man under normal condition and in right heart failure Am J Physiol 136 115 1942
18 Goodman L and Gilman A The pharmacological basis of therapeutics ed 2 New York 1955 The Macmillan Company
19 McMichael J Cardiotonics and diuretics in human heart failure J Chron Dis 9 602 1959
20 Gold H and Cattell McK Mechanisms of digitalis action in abolishing heart failure Arch Int Med 65 263 1940
21 Kay C F The clinical of digitalis preparations Circulation 12 116 1955
2 Stewart H J Crane N F Deitrick J E and Thompson W P Action of digitalis in compensated heart disease Arch I t Med 62 547 1938
23 Cohn A E and Stewart H J E idence that digitalis influences contraction of the heart in man J Clin Invest 1 97 1924
24 Stewart H J and Cohn A E Studies on the effect of the action of digitalis on the output of blood from the heart J Clin Invest 11 917 1932
25 Harrison T R Principles of internal medicine New York 1958 McGraw Hill Book Company Inc
26 Stewart H J Deitrick J E Crane N F and Wheeler C H Action of digitalis in uncompensated heart disease Arch I t Med 62 569 1938
27 Cohn A E and Steele J M Studies on the effect of the action of digital s on the output of blood from the human heart J Clin Invest 11 871 1932
28 LaDue J S and Fahr G Effect of intravenous administration of lanatoside C upon output diastolic olume and mechanical efficiency of failing human heart Am Heart J 25 344 1943
29 Nylin G On the amou t of and changes in the residual blood of the heart Am Heart J 2 598 1949
30 Lown B and Levine S A Current concepts in digitalis therapy Boston 1954 Little Brown & Company
31 Wood P Diseases of the heart and circulation Philadelphia 1957 J B Lippincott Company
3 Ferrer M I and Harvey R M The etiology of secondary pulmonary hypertension Bull New York Acad Med 30 208 1954
33 Capeller D on Copeland G D and Stern T U Digitalis intoxication A clinical report of 148 cases Ann I t Med 50 869 1959
34 Marriott H The ascendency of digitoxin nd renaissance of gital Ann Int Med 40 870 1954
35 K er F A The role of digitalis intoxication in refractory heart failure Quart B ll Northwestern Uni Med School 29 158 1955
36 Clinical Conferences Digitalis intoxication Circulation 9 115 1954
37 Batterman R C and Gutner L B Increasing congestive fail re A manifestation of digitalis toxicity Circulation 1 1052 1950

Kinetocardiographic alterations in patients with congestive heart failure at rest and after exercise
The effect of digitalis

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Having previously reported the effects of heart failure on the kinetocardiogram as determined during the resting state, we now report on the changes produced by physical effort in patients with heart failure as compared to normal subjects. The effectiveness of digitalis in preventing these exercise-induced alterations will also be reported.

Methods

Recordings of low frequency precordial movements (kinetocardiogram, KCG) were made with the bellows-crossbar technique, using a 6-channel Sanborn direct writer. ECG and carotid pulse curves were simultaneously obtained. All tracings were recorded at the end of a normal expiration and from the fourth intercostal space in the left parasternal line.

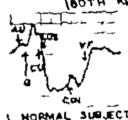
After control resting tracings were taken, each patient was exercised from 30 seconds to 2 minutes, depending on the clinical status; 2 minutes of exertion were used for all normal subjects. This physical effort consisted of moving, while the subject was recumbent, a 10 pound pulley weight system a distance of 8 feet every 3 seconds. Recordings were made at ½, 1, 2, 4, 6, 8, and 10 minutes after completion of the exercise.

Two movements were considered: first, an outward (upward) deflection occurring at the time of atrial systole; second, an inward (downward) motion appearing at the time of rapid ventricular ejection. Both were expressed as a percentage of total amplitude (TA), the latter being determined by measuring the distance from the highest to the lowest point of a complete cardiac cycle complex (Fig. 1).

The measurement of the ejection downstroke (EDS) was readily achieved because in the precordial area studied this movement begins 0.12 to 0.16 second after the onset of ventricular excitation and at about the time of the start of the carotid upstroke. The separation of the atrial upstroke (AU) movement from the outward deflection due to passive ventricular filling (VF) presented some difficulty when the rate was rapid. Under these circumstances, filling may start after the onset of the P wave, and the two outward motions may be fused. Consequently, only those complexes were studied which presented two distinct upward

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*Predoctoral fellows of the United States Public Health Service.
**[illegible]

A RECORDS FROM A NORMAL SUBJECT AND A PATIENT WITH HEART FAILURE (BOTH RECORDED AT REST)





ALL RECORDS BEGIN AND WITH THE P WAVE OF THE ECG

TIME LINES = 0 02 SEC

1 NORMAL SUBJECT 2 PATIENT WITH CONGESTIVE FAILURE

B THE EFFECT OF EXERCISE ON KINETOCARDIOGRAMS FROM A PATIENT WITH CLASS III CONGESTIVE HEART FAILURE









1 RESTING CONTROL 2 ONE MINUTE AFTER EXERCISE 3 TWO MINUTES AFTER EXERCISE 4 SIX MINUTE AFTER EXERCISE

* NEW YORK HEART ASSOCIATION CLASSIFICATION

AU ATRIAL UPSTROKE EDS = VENTRICULAR EJECTION DOWNSTROKE TA TOTAL AMPLITUDE VF PASSIVE VENTRICULAR FILLING WAVE P = P WAVE OF ECG Q Q WAVE OF ECG CU CAROTID UPSTROKE CIN CAROTID INCISURAL NOTCH

Fig 1 This figure shows comparison of resting record obtained from normal subject and from patient with symptomatic congestive heart failure The effect of minimal exertion on kinetocardiograms from patient with Class III failure is shown (The patient was exercised for one minute while supine by using two 5 pound weights on pulley weight system These were moved distance of 8 feet every 3 seconds twenty complete pulls were attained) All records begin with the P wave of the ECG to better demonstrate the marked changes which occur in diastole 1 Comparison of resting kinetocardiograms 1 \ to the [illegible] [illegible] absent atrial upstroke (AU) motion the large passive ventricular filling wave (VF) and the prominent ventricular ejection downstroke (EDS) 2 The passive ventricular filling [illegible] is markedly reduced the atrial upstroke is quite large and the ejection downstroke is decreased in relation to the total amplitude B Effect of exercise on kinetocardiograms 1 This record could be considered normal since all movements studied are within normal limits 2 The record now be[illegible] abnormal The atrial movement has increased ejection downstroke decreased and the ventricular filling wave has changed little 3 The atrial movement has continued to increase the ejection downstroke remains decreased and the ventricular filling wave is markedly reduced 4 The record now has again become [illegible] normal

deflections with the second (atrial upstroke AU) starting 0 04 to 0 10 second after the beginning of atrial excitation

Three percentages were determined AU TA × 100 EDS TA × 100 and AU EDS × 100 Fig 1 shows the movements considered in this communication

Subjects

Normal values were obtained from 15 subjects who were over 35 years of age none of whom had any evidence of cardiac disease A total of 28 studies were performed on 22 patients with known heart disease these were given a classification of their cardiac status according to stand-ards established by the New York Heart Association[4] Each was independently evaluated by two or more observers before any studies were initiated

Thus this report includes studies on 15 normal subjects 10 on patients with Class I 11 on patients with Class II 6 on patients with Class III and 1 on a patient with Class IV heart disease Table I presents the clinical data on the patients Four were studied before during and after digitalization so that the effects of exercise on kinetocardiograms from the same patient with varying degrees of compensation were recorded No record was included that was obtained at the time of anginal pain

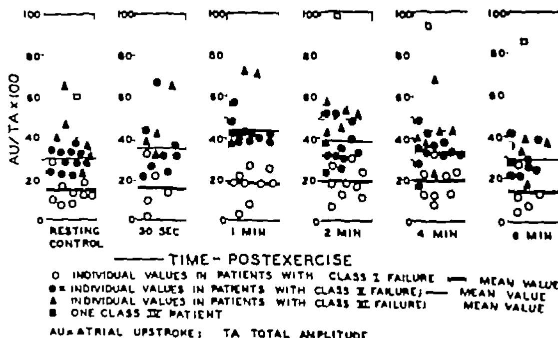


Fig. 2. This figure shows a comparison of the relative atrial upstroke amplitudes (AU/TA × 100) in the three groups of patients with cardiac disease that were studied (New York Heart Association Class I-III) both during the resting state and 30 seconds to 6 minutes after exertion. *Resting Control:* Overlapping occurs with all three groups. The range for the Class I patients was 8 to 29 per cent (mean 15 per cent), Class II 23 to 38 per cent (mean 30 per cent), and Class III 23 to 65 per cent (mean 40 per cent). *30 Seconds Postexercise:* Complete separation of the three groups does not occur, and the means show only minimal increase over control values. *1 Minute Postexercise:* Class II and Class III patients are now completely separated from Class I patients; the highest value for the Class I group is 26 per cent and the lowest for the Class II and Class III subjects 37 per cent. Mean values here show corresponding increase. *2 Minutes Postexercise:* Four of the Class II patients and all Class III patients are beyond the limit established for normal. All Class I subjects have continued to stay within the normal range. *4 Minutes Postexercise:* Four each of the Class II and Class III patients show values beyond the upper limits of normal; however, the mean value for the former group is now within the normal range. *6 Minutes Postexercise:* Three Class II and 2 Class III patients continue to show abnormal values. The mean value for each group is now in the normal range. Thus no separation of normal subjects and Class I patients can be made through the use of this criterion. Differentiation of both of these groups from Class II and Class III patients is possible when the changes in this root produced by exercise are evaluated. Note: Because of marked dyspnea, record could not be made from the one Class IV patient at ½ and 1 min after exertion.

Since patients with mitral or tricuspid valvular disease may have atrial distention and exaggerated atrial movements even in the absence of failure, such individuals were not studied.

Results

Each of the relative movements studied will be considered separately.

Atrial upstroke motion. The normal subjects and the group of patients with asymptomatic heart disease (Class I) showed no relative atrial outward movements greater than 30 per cent at rest or 33 per cent after exercise (Table II). Forty-six per cent of the Class II and 83 per cent of the Class III patients had values in excess of 30 per cent at rest; after exercise, all had such relative motions greater than 33 per cent. Serial postexertional recordings (Fig. 2) showed that the greatest atrial upstroke total amplitude ratio occurred 1 minute after cessation of physical effort. Return to the resting control level varied from 2 to 8 minutes; 2 patients, one each in the Class III and Class IV groups, failed to reach their initial levels 10 minutes after exertion. Fig. 3 *A* compares the changes in wedge pressure produced by exercise in normal subjects and in patients with failure. Fig. 3 *B* shows a comparison of resting and postexertional atrial movements from normal subjects and from patients of each failure group studied. The Class II and Class III patients had resting percentages that were interspersed with normal ones; however

complete separation of these latter two groups from the normal subjects and Class I patients could be made on the basis of this movement 1 minute after physical effort Separation of Class II from Class III patients is not possible through the use of this criterion except perhaps in those with values in excess of 60 per cent However by means of the changes produced in this relative motion by exertion separation of the patients of Class I from those of Class II and Class III was possible

Ventricular ejection downstroke movement The resting mean value for this motion in normal subjects was 62 per cent at rest and 55 per cent at 1 minute postexercise This pattern of essentially no change from control percentages after physical effort was seen in each group studied However it is obvious (Fig 4) that this relative motion decreases markedly with each successive increase in the severity of failure even though no consistent difference exists between the resting and postexertional state

Atrial upstroke–ventricular ejection downstroke ratio $(AU/EDS \times 100)$ Table II shows ranges and means for this parameter before and after exercise in the normal subjects and in patients with Class I to Class III heart disease An arbitrary value of 0 to 50 per cent was established as physiologic On the basis of this criterion 7 per cent of normal subjects 50 per cent of Class I 91 per cent of Class II and 100 per cent of Class III patients had values in excess of 50 per cent after exercise Thus this parameter proved to be the only one used that allowed even a beginning separation of normal from Class I subjects

Effect of digitalis on kinetocardiograms Table III shows a varying amount of decrease in the AU/TA ratios after the administration of digitalis to the 4 patients studied in this manner Fig 5 shows results

Table I *Clinical data on patients studied*

Name	Age (yr)	Sex	Diagnosis	Therapy	Classification†	Vital capacity (% normal)
J J	56	M	CAD	Digitalis	I	—
M R	69	M	CAD	Digitalis	I	73
J W	59	M	AI	Digitalis	I	74
L P	15	F	EC	None	I	—
N W	66	M	CAD	None	I	79
E M	51	M	AI	Digitalis	I	—
L H	43	F	HHD	None	I	84
J W	15	M	ASD	None	I	—
C H	12	M	ASD	None	I	93
O W	50	M	AS	None	I	—
W F	52	M	AI	Digitalis	II	56
M D	60	F	CAD	None	II	75
M S	44	F	Myocarditis	Digitalis	II	68
M N	70	F	CAD	Digitalis	II	75
M R	69	M	CAD	Digitalis	II	68
M D	60	F	CAD	Digitalis	II	75
J W	59	M	AI	Digitalis	II	65
J M	26	M	AI	Digitalis	II	70
A C	45	M	Pericarditis	Digitalis	II	70
H A	59	M	HHD	Digitalis	II	83
D C	57	M	AI	Digitalis	II	86
W K	52	M	AI	Digitalis	III	56
J F	61	M	CAD	Digitalis	III	85
H W	55	M	CAD	Digitalis	III	—
F O	63	M	CAD	Digitalis	III	88
J W	59	M	AI	Digitalis	III	46
J M	26	M	AI	Digitalis	III	61
J J	46	M	Myocarditis	Digitalis	IV	—

[illegible] of the [illegible]
†Classification [illegible] New York Heart Association
CAD Coronary artery disease AI Aortic insufficiency EC [illegible] complex HHD Hypertensive heart disease ASD Atrial septal defect AS Aortic stenosis

*Table II Range and means for each parameter studied in normal subjects and patients with Class I III heart disease**

Parameter			Normal (15 subjects)	Class I (10 patients)	Class II (11 patient)	Class III (6 patients)
AU/TA × 100	Resting control	Range	0–27%	8–29%	23–38%	23–65%
		Mean	12%	15%	30%	40%
		Comment	None > 30%	Non > 30%	5 > 30%	5 > 30%
	1 min post exercise	Range	0–33%	7–26%	37 57%	38–72%
		Mean	16%	19%	43%	55%
		Comment	None > 33%	None > 33%	All > 33%	All > 33%
EDS/TA × 100	Resting control	Range	24–96%	17–80%	5–67%	0–65%
		Mean	62%	49%	38%	26%
		Comment	3 < 50%	4 < 50%	8 < 50%	4 < 50%
	1 min post exercise	Range	21–92%	6–74%	2–91%	0–45%
		Mean	55%	39%	39%	23%
		Comment	6 < 50%	5 < 50%	9 < 50%	All < 50%
AU/EDS × 100	Resting control	Range	0–83%	10–71%	28–1 000+%	35–1 000+%
		Mean	21%	33%	201%	151%
		Comment	1 > 50%	2 > 50%	9 > 50%	5 > 50%
	1 min post exercise	Range	0–155%	10–120%	37 1 000+%	160–1 000+%
		Mean	30%	59%	192%	239%
		Comment	1 > 50%	5 > 50%	10 > 50%	All > 50%

*New York Heart Association classification

AU Atrial upstroke EDS Ventricular ejection downstroke TA Total amplitude

Table III Relative atrial upstroke amplitudes (AU/TA × 100) at rest and after exercise before and after digitalization

Patient	Control		1 min postexercise		2 min postexercise		4 min postexercise		8 min postexercise		Vital capacity (% normal)		Total amount of digitalis ([illegible])
	BD	AD	BD	AD	BD	AD	BD	AD	BD	AD	BD	AD	
J W	65	13	0	2	58	19	69	9	70	9	46	74	11 0 mg
W K	30	24	—	57	52	52	40	27	37	32	56	56	5 0 mg
M R	23	19	39	19	31	24	33	24	22	22	68	73	7 0 mg
J M	40	31	—	43	45	35	44	35	46	35	61	70	7 0 mg
Mean	39 3	2 5	55	22	46	32	46	24	44	25	58	68	

BD and AD Before and after digitalization respectively AU Atrial upstroke TA Total amplitude

obtained from one patient at different levels of compensation after various amounts of the drug This patient who after digitalization exhibited the most striking rise in vital capacity also showed a marked decrease in relative atrial motions The 3 patients who displayed little or no rise in vital capacity showed less impressive evidence of improvement in this KCG deflection

Discussion

This study has revealed that a marked exaggeration in kinetocardiographic atrial movements occurs after minimal effort in those patients with Class II and Class III heart disease Resting values for this motion were normal in some of the Class II and Class III patients whereas *all* demonstrated exaggerated atrial deflections after exercise The ventricular ejection down

stroke was noted to be decreased in these same patients while at rest with no consistent further decrease after effort. No marked change occurred in normal and Class I subjects. Thus confirmation is offered for earlier observations on kinetocardiograms obtained from patients with heart failure.

Previous work done in this laboratory attributed the increased relative atrial movements that occur in patients with failure to atrial distention resulting from an increase in ventricular diastolic pressure. This produces an increased vigor of atrial contraction and thus an increased amplitude of recorded atrial movements. Similarly the decrease in ventricular ejection downstroke was attributed to decreased contractility, cardiac output, and change of volume as ventricular ejection occurs.

An explanation for the increase in atrial movements which occurs and persists *after* exertion could possibly reside in a relationship to venous pressure. This in turn appears to be related to changes in oxygen supply and peripheral anaerobic metabolism. Therefore changes in venous pressure and in tissue metabolism which are known to occur in heart failure will be briefly presented.

That the degree of rise of peripheral venous pressure after exercise is well correlated with the severity of failure has been shown.[4] Richards[8] found that in contradistinction to normal subjects patients with failure have essentially no gradient between peripheral and central venous pressures. Atrial pressure in man has been shown to increase with failure irrespective of change in cardiac output,[9] and many with normal resting pressures develop abnormal values after exertion. This phenomenon has also been observed in the experimental animal.[10] Not only does venous pressure increase, it remains elevated for a longer period of time. Our study showed that the greater the degree of failure the longer were the atrial movements exaggerated. Thus the duration of elevation of these deflections apparently reflects the

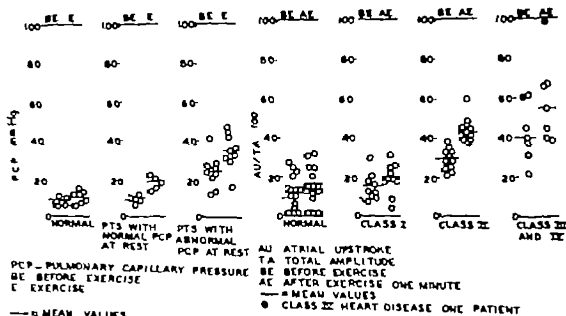


Fig. 3. *A*, The effect of exercise on the pulmonary capillary (wedge) pressure in normal subjects and in patients with congestive heart failure (data of Dexter et al. and Lewis et al.[10]). Note that 4 of 5 patients with normal wedge pressures at rest developed [illegible] increase in this measurement with exercise. All but one patient of the group with an abnormal wedge pressure at rest had an increase in [illegible] pressure [illegible] with exercise. *B*, Postexercise ratio of atrial upstroke movements to total amplitude ($AU/TA \times 100$) in normal subjects and in patients with Class I-IV congestive heart failure (New York Heart Association classification). Note that no essential difference exists between the normal subjects and Class I patients. Forty six per cent of Class II and 63 per cent of the Class III patients had abnormal resting values; after exercise all had atrial movements which exceeded normal limits.

status of the ventricular reserve capacity, i.e., the rapidity of recovery after exertion. Fig. 5 demonstrates this. In this patient the administration of digitalis first resulted in normal resting atrial movements. Postexertional values were abnormal but for only 5 minutes of the 10 minute study period. Before digitalis was given these values were exaggerated during the entire study period. Larger amounts of the drug resulted in normal values both before and after exercise.

Ford and associates[4] demonstrated that the greater cost of exercise is deferred to the recovery period in patients with cardiac disease. Thus the increased atrial movements seen in this study appear to be the result of *an inability of the ventricles to meet the inflow load during the recovery phase of exercise*. It is known that higher levels of blood lactic acid have been found in patients with failure than in normal subjects[...] and this difference increases with

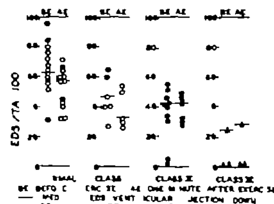


Fig. 4. This figure compares the pre- and postexertional ventricular ejection downstroke values (EDS/TA × 100) in the four groups studied (normal subjects to Class III cardiac patients). *Normal*: This value ranged from [illegible] to 96 per cent before exercise and from [illegible] to 9[illegible] per cent at 1 minute after exercise. Three values at rest and six after exertion were below 50 per cent. *Class I*: The resting range was 17 to [illegible]0 per cent, with five values below 50 per cent. After exercise the range was 6 to 67 per cent, with five below 50 per cent. *Class II*: Ranges were 5 to 67 per cent and 2 to 91 per cent at rest and after exertion, respectively. Three values at rest and two after exercise were above 50 per cent. *Class III*: Only one value at rest and none after exercise were above 50 per cent. Little change occurred in the postexertional state when compared with the resting state; however, median values showed a progressive decrease from the normal to the Class III group. (Classification of heart failure according to the New York Heart Association.)

exertion. A delayed return of the level of blood lactate to resting values was noted. Regan and associates[?] found a reduction in arterial venous lactate difference within 15 minutes after the administration of acetylstrophanthidin to patients with heart failure.

Huckabee and associates[7,18] found that patients with Class I heart disease had adequate oxygen transport with mild exercise and that the rate of lactate accumulation or rate of anaerobic metabolism was no different from that of normal subjects. In this type of patient the body tissues had to rely on anaerobic metabolism to only a small extent. In patients with definite failure (Class II or greater), oxygen transport was only 50 to 80 per cent effective in meeting body requirements, and a further increase in cardiac output of 40 to 90 per cent would have been necessary to effect such. It was the conclusion of these authors that during exercise most patients with failure have an inadequacy of oxygen supply rates to satisfy tissue energy requirements, and this in turn was due to an insufficient cardiac response. Our studies showed that normal subjects and Class I patients had very similar responses as regard atrial motions, whereas the reverse was true when an impairment of Class II or greater existed. On the basis of Huckabee's work the duration of elevation of these movements may perhaps be interpreted as a reflection of the ability of the ventricles to empty themselves and thereby to supply tissue oxygen, i.e., the longer the elevation, the higher the ventricular diastolic pressure and the worse the failure.

The dramatic reversal of abnormal motions which may occur after digitalis (Fig. 5) can be attributed to the increase in myocardial contractility effected by this drug. Thus ventricular emptying is enhanced and residual volume is decreased, as is ventricular diastolic pressure; the resultant is a decrease in atrial distention and pressure. The ventricle can now meet the inflow load presented it during the postexercise period.

The changes in precordial motions produced by exercise appear to be related to heart failure and not to heart disease. This would offer an explanation for the absence of changes in Class I patients and the

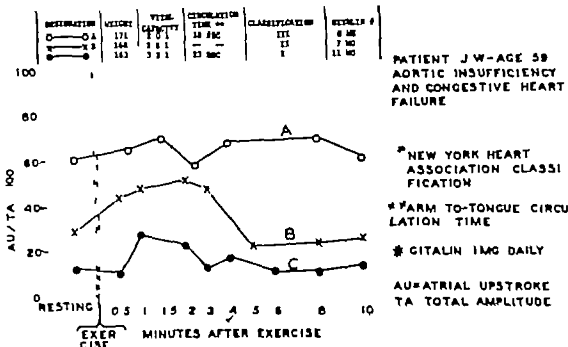


Fig 3 Relative atrial upstroke amplitudes (AU/TA × 100) in one patient at the same level of exercise before during and after digitalization The patient was admitted to this study at a time when he was receiving small daily dose of digitalis but was for all practical purposes totally undigitalized *A* Initial study The values are all grossly abnormal Clinically the patient was considered to be in Class III vital capacity was reduced and circulation time prolonged *B* After 7 0 mg of oral gitalin vital capacity showed increase weight decreased 3 pounds and clinically the patient was less incapacitated Atrial movements at rest were within normal limits but after exercise they were definitely abnormal for 5 minutes of the 10-minute study *C* After 11 0 mg of oral gitalin Control and postexertional relative atrial movements were all within the range established for normal A total increase in vital capacity of 1 2 liters decrease in arm to-tongue circulation time of 5 seconds and decrease in weight of 8 pounds occurred

presence of such alterations in the more advanced classes Thus small amounts of effort in patients with symptomatic decompensation are readily reflected by an exaggeration of relative atrial deflections these in turn reflect atrial pressure and distention In addition the effect of digitalis can be at least partially observed through the use of this method

Summary

1 Twenty-eight studies were done on 22 patients with cardiac disease who varied from asymptomatic (Class I) to definitely decompensated (Class II or greater) The results were compared with those in 15 normal individuals

2 Class-I patients had normal resting and postexertional relative atrial movements Forty six per cent of Class II and 83 per cent of Class III patients had abnormal atrial movements at rest after exercise all showed values in excess of those established for normal An explanation is postulated for this finding

3 Four patients were given varying amounts of digitalis after which studies were made during the resting and post exertional state All showed a reduction of the exaggerated atrial movements in 1 a marked change occurred in 2 a moderate change and in 1 only a slight decrease was noted In each however a tendency toward an increased tolerance to exercise was noted

4 Changes in precordial movements as determined by this method are in remarkable agreement with those determined by the more complex procedure of cardiac catheterization with measurement of wedge and other pressures

REFERENCES

1 Skinner N S J Kinetocardiographic findings in patients with congestive heart failure and changes after therapeutic digitalization Am Heart J 61 445 1961

Table I. Number of ECGs taken at each age in each of the three groups

	A (1 day old)	B (6 wk old)	C (3 mo old)
Group I (800-1,300 grams)	16	12	5
Group II (1,300-1,800 grams)	36	20	9
Group III (1,800-2,300 grams)	91	48	13

Table II. Mean heart rate ± standard deviation (beats per minute)

	A	B	C
Group I	140 (± 11)	180 (± 16)	174 (± 18)
Group II	140 (± 11)	177 (± 8)	180 (± 11)
Group III	135 (± 28)	166 (± 17)	177 (± 24)

Table III. P-R interval (seconds) ± standard deviation

	A	B	C
Group I	0.11 ± 0.01	0.11 ± 0.02	0.11 ± 0.01
Group II	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01
Group III	0.11 ± 0.02	0.11 ± 0.01	0.12 ± 0.01

to maturation was registered in the electrocardiogram as the infants grew older. The first group consisted of 16 infants who weighed between 800 and 1,300 grams. In this group, 70 per cent were females and 30 were males; 92 per cent were non-white. Twelve of these infants had two electrocardiograms taken at 1 day of age and again at 6 weeks of age. 5 patients of this group also had a third electrocardiogram taken at 3 months of age. The second group consisted of 36 infants who weighed between 1,300 and 1,800 grams. In this group, 50 per cent of the patients were males and 50 per cent were females; 98 per cent were non-white. Twenty of this group of patients had two electrocardiograms taken at 1 day of age and at 6 weeks of age, and 9 of these infants had a third electrocardiogram taken at 3 months of age. The third group consisted of 91 infants who weighed between 1,800 and 2,300 grams. In this group, 40 per cent were males and 60 per cent were females; 98 per cent were non-white. Forty-eight of these infants had two electrocardiograms taken on the first day of life and again at 6 weeks of age, and 13 of these had a third electrocardiogram taken at 3 months of age. (See Table I.)

The following parameters have been studied: The heart rate, the P-R interval, the Q-T interval, the corrected Q-T interval (Q-T$_c$), and the Q-T ratio $\frac{Q\text{-}T}{Q\text{-}T_c}$, the QRS duration usually measured in Lead V_1, the axis of the P wave in the frontal plane (ÂP), the axis of the QRS complex in the frontal plane (ÂQRS), the height of the R wave in millivolts in Leads V_{4R}, V_1, and V_6, the ratio of the height of the R wave to that of the S wave in Leads V_{4R} and V_1 (R/S_{V4R} + R/S_{V1}), and the greatest total voltage in millivolts of the R wave plus the S wave measured in Lead V_1 to Lead V_6.

The letters A, B, and C were used to designate the age of the infant. A signified the first day of life, B indicated 6 weeks of age, and C was used for 3 months of age. Representative electrocardiograms from the three groups of patients are shown in Figs. 1-3.

Rate (Table II) and rhythm. All of the infants in this study had sinus rhythm. One patient had multiple arrhythmias which reverted to a sinus arrhythmia when she was 3 months old. It was not possible to completely rule out heart disease in this baby, and for that reason the patient was not included in this report. The mean heart rate on the first day of life was 140 (± 11) beats per minute in Group IA and Group IIA (infants who weighed from 800 to 1,800 grams). In Group IIIA (infants who weighed from 1,800 to 2,300 grams) the mean heart rate on the first day of life was 135 (± 28) per minute. This was a greater range than for the smaller premature babies. There was no significant difference in heart rate for the infants in Groups IB, IIB, and IIIB at 6 weeks of age nor in Groups IC, IIC, and IIIC at 3 months of age.

P-R interval (Table III) and axis of the P wave in the frontal plane (Table IX). The mean value of the P-R interval was 0.11 second in all age groups and at all weights except for the largest premature babies at 3 months of age, Group IIIC. The latter

Table IV Mean Q T interval (seconds) ± standard deviation

	A	*B*	*C*
Group I	0 28 ± 0 05	0 23 ± 0 01	0 6 ± 0 02
Group II	0 28 ± 0 05	0 22 ± 0 03	0 23 ± 0 02
Group III	0 30 ± 0 03	0 24 ± 0 0	0 24 ± 0 02

Table V Mean Q T (seconds) ± standard deviation

	A	*B*	*C*
Group I	0 44 ± 0 03	0 39 ± 0 0	0 43 ± 0 01
Group II	0 4 ± 0 0	0 38 ± 0 07	0 40 ± 0 02
Group III	0 44 ± 0 07	0 40 ± 0 01	0 40 ± 0 02

Table VI Mean Q T ratio $\left(\frac{QT}{QT}\right)$ ± *standard deviation*

	A	*B*	*C*
Group I	1 09 ± 0 17	0 99 ± 0 03	1 07 ± 0 02
Group II	1 06 ± 0 0	0 96 ± 0 07	1 00 ± 0 03
Group III	1 09 ± 0 09	1 00 ± 0 08	1 00 ± 0 05

Table VII Mean duration of QRS measured in Lead V_1 *(seconds) ± standard deviation*

	A	*B*	*C*
Group I	0 036 ± 0 008	0 038 ± 0 004	0 040 ± 0 001
Group II	0 036 ± 0 007	0 037 ± 0 010	0 039 ± 0 006
Group III	0 037 ± 0 007	0 036 ± 0 007	0 038 ± 0 007

Table VIII Mean AQRS (measured in degrees) ± standard deviation

	A	*B*	*C*
Group I	103 ± 22	84 ± 34	63 ± 12
Group II	124 ± 20	85 ± 28	8 ± 28
Group III	12 ± 29	85 ± 19	70 ± 19

group of patients had a mean P R interval of 0 12 second which closely approximated full term infants of similar age [8] There was no evidence of first-degree atrioventricular block in an of the premature infants studied The P wave in the limb leads of the electrocardiogram on the first day of life usually was of higher amplitude and was peaked in the smaller premature infants The mean axis of the P wave in the frontal plane was constant and varied only slightly in all age and weight groups Usually it was 60 degrees

Q T interval (Table IV) Q T interval corrected (Q T) (Table V) and Q T ratio (Table VI) The mean value of the Q T interval was prolonged on the first day of life The mean value of the Q T (corrected Q T interval) on the first day of life was 0 44 second in Groups IA and IIIA and 0 42 second in Group IIA The Q T ratio $\frac{QT}{QT}$ more accurately reflected prolongation of Q T The mean value of the Q T ratio was 1 09 in Group IA 1 06 in Group IB and 1 09 in Group IC whereas in 6 week-old infants the mean Q T ratio was 0 99 in Group IIA 0 96 in IIB and 1 00 in Group IIIA The mean Q T ratio in 3 month-old infants was 1 00 in Groups IIIB and IIIC The mean Q T ratio in Group IIIC was 1 07 and may not have reflected the true value since only 5 patients were studied

Duration of the QRS complex usually measured in Lead V (Table VII) and axis of the QRS complex in the frontal plane (ÂQRS) (Table VIII) The duration of the

Table IX Mean axis of P wave (measured in degrees) ± standard deviation

	A	*B*	*C*
Group I	60 (± 2)	60 (± 2)	59 (± 1)
Group II	60 (± 2)	59 (± 2)	60 (± 1)
Group III	61 (± 2)	60 (± 2)	60 (± 1)

Table X Mean R S ratio in Lead V_{4R} ± *standard deviation*

	A	*B*	*C*
Group I	3 5 ± 2 0	3 2 ± 2 8	2 1 ± 2 0
Group II	2 4 ± 1 9	3 1 ± 2 0	2 3 ± 1 6
Group III	2 8 ± 2 7	3 9 ± 3 5	2 ± 1 5

Table XI Mean R/S ratio in Lead V_1 ± *standard deviation*

	A	*B*	*C*
Group I	1 5 ± 1 3	2 4 ± 2 0	2 7 ± 0 8
Group II	1 4 ± 1 2	1 6 ± 1 0	1 5 ± 1 0
Group III	1 9 ± 1 9	2 3 ± 1 4	1 3 ± 0 9

Table XII Mean height of R wave in Leads V_{4R}, V_1 and V_6 (in millivolts) ± standard deviation

	A			B			C		
	V_{4R}	V_1	V_6	V_{4R}	V_1	V_6	V_{4R}	V_1	V_6
Group I	(±3)	8 (±2)	5 (±3)	10 (±6)	9 (±4)	10 (±6)	7 (±2)	14 (±4)	15 (±3)
Group II	7 (±1)	7 (±4)	7 (±3)	7 (±3)	10 (±3)	1 (±6)	7 (±4)	10 (±5)	12 (±7)
Group III	7 (±3)	9 (±2)	6 (±4)	6 (±2)	9 (±2)	10 (±6)	7 (±2)	10 (±3)	14 (±5)

QRS complex as usually measured in Lead V_1 had a consistent set of values on the first day of life. The minimum value was 0.02 second in Groups IA and IIA and 0.30 second in Group IIIA. The maximum value in Group IIIA was 0.06 second and there was no other measurement that exceeded this. The mean values for all groups at all ages was fairly constant.

The axis of the QRS complex in the frontal plane (ÂQRS) followed a similar pattern. On the first day of life the mean values were 103 (± 22 degrees) in Group IA, 124 (± 20 degrees) in Group IIA, and 122 (± 29 degrees) in Group IIIA. There was a shift in ÂQRS to the left at 6 weeks of age as shown in the tracings and a smaller shift to the left as demonstrated by the mean values of ÂQRS at 3 months of age.

Ratio of R/S in Leads V_{4R} and V_1 (Tables X and XI), height of R wave in Leads V_{4R}, V_1 and V_6 (Table XII), greatest total voltage of the R+S waves measured in Leads V_1 to V_6 (Table XIII). There was a slight decline in the R/S ratio in Lead V_{4R} as the infant grew from the time of birth to 3 months of age. The height of the R wave in Lead V_{4R} did not change significantly from birth to 3 months of age; therefore the decline in this ratio was due to an increase in the S wave in the electrocardiogram of these patients at 3 months of age.

Table XIII Mean ± standard deviation. Greatest total voltage of R+S measured in Lead V_1 to V_6

	A	B	C
Group I	23 ± 9	28 ± 4	33 ± 7
Group II	26 ± 9	27 ± 6	31 ± 6
Group III	27 ±	28 ± 9	31 ± 6

At birth the R waves in Leads V_{4R} and in Lead V_6 were of comparable height. There was a somewhat taller R wave in Lead V_1 than in Leads V_{4R} and V_6. The R wave in Lead V_6 of the electrocardiogram increased slightly in height in all groups as the infant grew from birth to 3 months of age.

In the first 24 hours of life many premature infants had an R/S ratio in the right precordial leads of less than 1.0. This indicated that the S wave was of greater amplitude than the R wave. This pattern was present in 25 per cent of the infants in Group IA, in 36 per cent of the infants in Group IIA, and in 39 per cent of the infants in Group IIIA. As the infant matured from 6 weeks to 3 months of age the pattern changed and the R wave in the right precordial leads became equal to or larger than the S wave.

The mean value of the greatest total voltage of the R+S waves measured in Lead V_1 to Lead V_6 varied only slightly in all of the infants studied. It was well below the value of 50, which is given as top normal in full term infants and in children.[1]

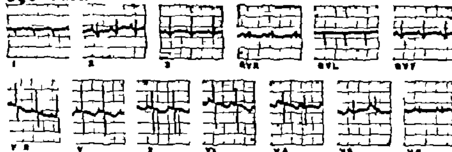
T wave and RS-T segment. In a great majority of the electrocardiograms of all the premature infants the T waves were inverted in the right precordial leads and upright in the left precordial leads. There were no patients in Group IA (infants who weighed from 800 to 1,300 grams) who had upright T waves on the first day of life. Three per cent of the infants in Group IIA and 13 per cent of those in Group IIIA had upright T waves in the right as well as in the left precordial leads at birth. When the infants were 6 weeks of age all of the electrocardiograms showed inverted T waves in the right precordial leads.

The RS-T segment was isoelectric in nearly all of the electrocardiograms taken

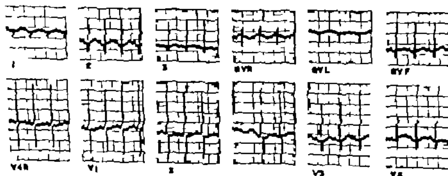
Discussion

The typical electrocardiogram of the premature infant showed sinus rhythm at a mean heart rate of 135 (± 28). There was no great difference in heart rate due to the weight of the baby at birth. Ziegler gave a heart rate of 115 to 130 in full term infants on the first day of life. Vanoni's series of premature infants[1] had a mean heart rate of 135 per minute on the first day of life. The mean heart rate increased at 6 weeks of age but remained at that level at 3 months of age. There was no significant difference in heart rate among the three groups at the various birth weights at 6 weeks of age and at 3 months of age. All of the infants at 6 weeks of age and at 3 months of age had sinus rhythm and no arrhythmias were encountered.

The mean P-R interval was 0.11 second in all groups except Group IIIC. This group had a P-R interval of 0.12 second. This agreed with the result in earlier studies[3,4] in full term infants. However



6 WEEKS



3 MONTHS

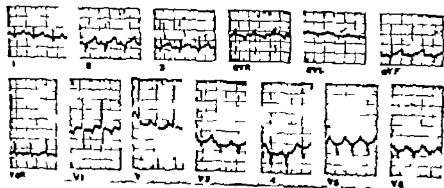


Fig. 1. Group I. Patient D. G. Birth weight of 1,250 grams.

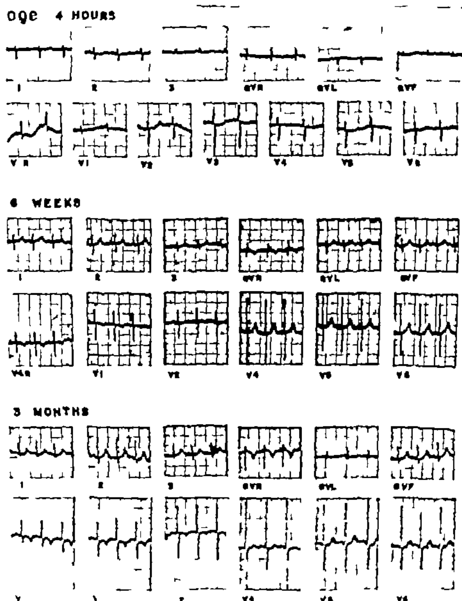


Fig. 2. Group II. Patient K. C. Birth weight of 1,751 grams.

Heck gave a shorter P-R interval, 0.092 second, at 1 day of age in his premature infants.

The P waves were usually peaked with voltage up to 2.5 or 3.0 mm. on the first day of life with a duration of 0.05 and 0.07 second. The so-called "P pulmonale" on the first day of life may have represented higher pressures in the pulmonic circuit which are reflected in the atria. The axis of the P wave is very constant at 60 degrees. There was little variation at any age and weight. This was confirmed in earlier studies.[11,13,14]

The Q-T interval on the first day of life was slightly prolonged. Body temperature did not play a great part in this, because all of the premature babies studied had stabilized body temperature above 37°C. There are many factors which may prolong the Q-T interval, among which are hypocalcemia and anoxia, as well as hypothermia.[1] Therefore, a prolonged Q-T interval may occur with a normal QRS interval or with a prolonged QRS interval.[1] In these cases, the QRS interval on the first day of life was not prolonged, and [illegible] that a change had occurred in

the time that it took the stimulated ventricles to return to the resting state

The mean manifest electrical axis of the QRS complex measured in the frontal plane followed the same pattern as that found in earlier studies[2] [14] There was no essential difference in any of the weight groups studied on the first day of life There was a change in mean ÂQRS with a shift to the left at 6 weeks and a small shift at 3 months

The measurements of the height of the R waves in Leads V_{4R} V_1 and V as well as the R/S ratio in Leads V_{4R} and V and the total of the R+S waves measured in its greatest height in Leads V_2 and V will be most helpful in the diagnosis of right ventricular hypertrophy in the newborn premature infant It was apparent from this study that a well formed R wave was present in Lead V_4 on the first day and was of equal height with that found in Lead V_{4R} and that the R wave was taller in Lead V_1 The S wave increased in Lead V_{4R} as the infant grew from birth to 3 months of age

In an earlier study[8] of the ECG of the newborn full term infant it was noted that the R/S ratio in the right precordial leads was less than 1 in a number of the infants

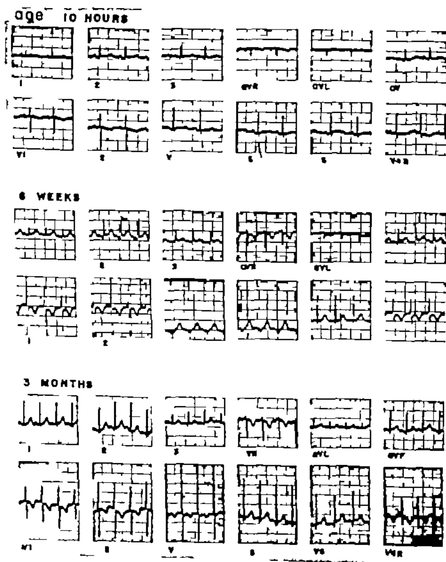


Fig 3 Group III Patient M C. Birth weight of 2 136 grams

studied In premature infants this pattern also was found in a significant percentage of the infants studied on the first day of life and it was noted that the R S ratio more nearly approached 1 0 as these infants grew older The R wave was well developed in Lead V_6 on the first day of life and indicated a difference from that of full term infants at that age De la Cruz (cited by Sodi Pallares and associates[17]) studied 70 normal hearts of infants and children who ranged in age from 6 months of intrauterine life to 11 years and showed that the thickness of the free wall of the right ventricle is less than that of the left ventricle These anatomic findings are not contrary to the morphology recorded in right (V_{4R} V_1 V) and left (V and V_6) precordial leads in these premature infants

The greatest total voltage of R+S measured in Lead V_1 to Lead V never approached the level of the pathologic which had been found in an earlier study on ventricular septal defects

It was stated in an earlier study that the T waves are upright in the right precordial leads and frequently inverted in the left precordial leads during the first hours or in the first days of life In this study in the smallest group of premature infants (weight of 800 1 300 grams) no ECG was found that had upright T waves in the right precordial leads nor inverted T waves in the left precordial leads In the second group of infants (Group IIA weight of 1 300 1 800 grams) only 3 per cent had upright T waves in the right precordial leads during the first 24 hours of life none of these infants had inverted T waves in the left precordial leads In the infants who ranged in weight between 1 800 and 2 300 grams 13 per cent had upright T waves in the right precordial leads and none had inverted T waves in the left precordial leads By 6 weeks of age there was a change in all of the electrocardiograms to inverted T waves in the right precordial leads In a screening study done on normal premature infants of all weights those infants who had had upright T waves in the right precordial leads on the first day of life all showed normally inverted T waves by the third day of life [4] This finding agreed with the results of the earlier studies of European workers [11 r]

Summary and Conclusions

1 Electrocardiograms were taken on 143 normal premature infants on the first day of life at 6 weeks and again at 3 months The infants were divided into three groups on the basis of their weight at birth

2 All patients had normal sinus rhythm at an average rate of 140 The mean P R interval was 0 11 second and the mean duration of QRS was between 0 36 and 0 40 second The ÂP was +60 degrees These findings were independent of birth weight and were unchanged from birth to 3 months of age

3 The ÂQRS was greater than +100 degrees at birth and showed a progressive leftward shift with age in all three groups This leftward shift was also evidenced by (a) the increasing amplitude of the S wave in Lead V_{4R} with age (b) the decreasing R S ratio in the right precordial leads with age and (c) the well developed R wave in Lead V_6 which increased in amplitude with age

4 There was a significant group of infants (38 per cent of the whole study material) who showed at birth an R S ratio of less than 1 in the right precordial leads With age this ratio tended to increase rather than decrease

5 The T wave in the left precordial leads was uniformly upright in all patients at all ages The majority of patients showed inverted T waves in the right precordial leads at birth and this too did not change up to 3 months of age Thirteen patients (1 in Group II and 12 in Group III) showed upright T waves in the right precordial leads which then subsequently inverted in all of these patients by 6 weeks of age

The author wishes to express his thanks to Miss Marion Siegel for her help in taking many of the electrocardiograms and to Dr David H Lewis who ted in the preparation of the manuscript

REFERENCES

1 Ziegler R F Electrocardiographic studies in normal infants and children Springfield Ill 1951 Charles C Thomas Publisher
2 Bharucha and Datey Electrocardiogram of infants Indian J Child Health 423 1955
3 Schaffer A J Burnstein J Mascia A V Barenberg P L and Stillman N The unipolar electrocardiogram of the newborn infant Am Heart J 39 383 1950

4. Ziegler R. F. The importance of positive T waves in the right precordial electrocardiogram during the first year of life. Am. Heart J. 52:533 1956
5. Rothfeld E. L. Wachtel F. W. Kaylen W. S. and Bernstein A. The evolution of the vectorcardiogram and electrocardiogram of the normal infant I. The normal newborn. Am. J. Cardiol. 5:439 1960
6. Wachtel F. W. Rothfeld F. L. Kaylen W. S. and Bernstein A. The evolution of the vector cardiogram and electrocardiogram of the normal infant II. Transition toward adult patterns. Am. J. Cardiol. 5:450 1960
7. Rosen J. L. and Goldberg M. The electrocardiogram of the normal infant. Dis. Chest 22:493 19
8. Benedikt A. Das QT Intervall bei Frühgeborenen. Kinderärztl. Praxis (Leipzig) 26:546 1958
9. Radu C. E. Das Electrokardiogramm des Frühgeborenen. Acta paediat. Stockholm 18:140 1935
10. Stoermer J. Das Electrokardiogramm bei untergewichtigen Frühgeborenen. Wchnschr. Kinderhk. 103:386 1957
11. Angeli G. Rilievi electrocardiografici negli immaturi. Minerva ginec. (Torino) 8:936 1956
12. Vanoni R. P. Rilievi electrocardiografici nel neonato immaturo. Minerva pediat. (Torino) 10:1041 1958
13. Engel E. Das Electrokardiogramm gesunder Frühgeborener, Neugeborener und Säuglinge. Ztschr. Kinderh. 50:359 1937
14. Heck W. Stoermer J. and Joppich G. Pädiatrischer EKG—Atlas. Stuttgart 1959 Georg Thieme Verlag
15. Nelson W. E. Textbook of pediatrics. Philadelphia 1959 W. B. Saunders Company
16. Avalos de Landero C. A mathematical method to determine electrical axis. Am. Heart J. 44:67 1952
17. Sodi Pallares D. Portillo B. Cisneros F. De la Cruz M. V. and Acosta A. R. Electrocardiography in infants and children. Pediat. Clin. North America 5:3 5 8 6 1958
18. Lepeschkin E. Modern electrocardiography. Baltimore 1951 Williams & Wilkins Company
19. Dreifuss L. Bender S. Bentivoglio L. Downing D. and Goldberg H. Significance of right heart strain in 400 cases of congenital heart disease: hemodynamic correlation (Abstract). Circulation 16:8 3 1957
20. Hubsher J. Unpublished data.

Effects of posture, upright exercise, and myocardial stimulation on cardiac output in patients with diseases affecting diastolic filling and effective systolic ejection of the left ventricle

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Two patterns of cardiovascular responses to upright exercise of walking were found in previous studies of patients with heart diseases. The majority of individuals tested showed increases in heart rate, cardiac output, mean systemic arterial pressure, and arteriovenous oxygen difference as compared with the resting values observed when they were either recumbent or sitting upright. A minority of patients exhibited a faster heart rate, but less increase in cardiac output, because of a failure to raise stroke index above the sitting level; this was associated with a fall in arterial blood pressure designated as "exertional hypotension." Both groups of patients had a significant fall in stroke volume when they changed posture from supine to sitting upright. The effects of pathologic lesions primarily altering either diastolic filling or effective systolic ejection of the left ventricle have been investigated in further studies on comparative responses to postural changes, upright exercise, and myocardial stimulation. In this connection effective systolic ejection refers to the net forward flow through the aorta.

Circulatory adaptations to upright posture were described by McMichael and Sharpey-Schafer[2] in 1944. Although oxygen consumption increased slightly during standing, arteriovenous oxygen difference widened and cardiac output fell 25 per cent from a mean value during recumbency of 6.0 L./min. to a mean of 4.5 L./min.[2] More recently, Novy and associates[3] reported even greater decreases in cardiac output on motionless standing for 10 minutes. Presumably, these changes represent a redistribution of blood volume (which diminishes the pulmonary and increases the systemic venous reservoirs) in response to the stress of gravity in relation to the position of the body. Rushmer[4] has emphasized the importance of these postural changes in the evaluation of ventricular function during exercise in the erect position.

Although hyperkinemic responses to exercise have usually been attributed to

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increases in both heart rate and stroke volume. Rushmer recently has questioned the capacity of the stroke volume to increase above the resting recumbent value.[6] In human subjects, however, Musshoff and associates found both stroke volume and heart rate increased progressively with graded amounts of exercise performed during recumbency. Mitchell and associates[7] in studies of maximal oxygen consumption in normal subjects during exercise in the upright position found that both stroke volume and heart rate virtually doubled when compared with values obtained with the subjects standing at rest. Cross circulation experiments in dogs have identified both neural and humoral mechanisms for the hyperkinemia of exertion.[8] With respect to humoral agents, however, norepinephrine has been found to be significantly increased only at maximal work loads in human beings.

Since the synthetic catecholamine isoproterenol is more potent than either epinephrine or norepinephrine in increasing heart rate and contractile force in the isolated perfused heart of several mammalian species, it is an effective myocardial stimulant. It restores rhythmicity after reflexly induced standstill and accelerates ventricular rate in the presence of complete atrioventricular block.[11] It produces tachycardia in the intact dog, whereas comparable doses of epinephrine or norepinephrine produce bradycardia. In the isolated perfused canine heart, isoproterenol increases myocardial oxygen consumption without depleting stores of glycogen when employed in very minute doses that do not induce arrhythmias.[12] In human subjects, isoproterenol increases cardiac output and lowers pulmonary capillary pressure even in patients with congestive heart failure.[14] It increases stroke volume significantly ($p < .02$) in normal subjects in the supine position but less so ($p > .05$) when the head is tilted up 60 degrees.[15] Peripheral venous constriction with isoproterenol tends to redistribute blood volume from systemic to pulmonary venous reservoirs[6] and contributes to an increased central blood volume.[7] Since with progressively larger doses isoproterenol produces arrhythmias, conduction defects[13] and myocardial necrosis,[19] the use of this drug to stimulate the myocardium must be carefully supervised.

Material and methods

Fourteen patients with diseases affecting the chambers of the left side of the heart were studied in conjunction with diagnostic cardiac catheterization. Of the 8 females and 6 males, 7 patients had limitation of diastolic filling of the left ventricle due to mitral stenosis (confirmed surgically in all 6 who were operated upon), and 7 had lesions which reduced the effective systolic ejection of the left ventricle. Of the latter patients, 2 had predominant mitral regurgitation, 2 had aortic stenosis, and 1 each had aortic regurgitation, multivalvular rheumatic heart disease (without significant mitral stenosis), and hypertensive cardiovascular disease. Atrial fibrillation was present in 5 patients with mitral stenosis and in 2 with left ventricular diseases. All except 2 patients, one with aortic stenosis and another with mitral stenosis, were taking digitalis. The average functional capacity (Classes I to IV of the New York Heart Association) and physical fitness index of tolerance for a standardized exercise test were 3.0 and 7.1, respectively, for patients with mitral stenosis and 2.3 and 14.5, respectively, for patients with left ventricular disease. Thus, patients with mitral stenosis selected for this study tended to be more impaired both clinically and by exercise testing than the other patients.

Normal saline was injected subcutaneously for placebo sedation, and 2 per cent procaine was infiltrated for local anesthesia at the site of arterial and venous cut-downs. Arterial pressure and blood samples were obtained by a PE 90 polyethylene catheter inserted into the lumen of the radial artery; a No. 6F cardiac catheter was guided into the right pulmonary artery. Pressures were recorded with a Statham P23D transducer and Sanborn polygraph. Pressures were recorded continuously except during intermittent sampling and flushing of the catheters.

The oxygen content of samples of blood was determined by the method of Van Slyke-Neill. Oxygen consumption and ventilation were recorded while breathing oxygen with a 13.5 liter Collins rec

$$\text{(1) Resistance Index (dynes sec cm}^{-5} \times \text{M}^2) = \frac{(\textit{Mean Pressure})\ (1\,332)\ (60)}{\textit{Cardiac Index}}$$

$$\text{(2) LV work (Kg M /min /M}^2) = \frac{(\textit{Cardiac Index})\ (1\,065)\ (P_{SA} - 5)\ (13\,6)}{1\,000}$$

eter Cardiac output was determined by the direct Fick principle utilizing blood withdrawn from the pulmonary artery for the determination of mixed venous oxygen content Arterial samples were withdrawn simultaneously from the radial artery

Each patient served as his own control and responses to posture isoproterenol and exercise were determined Five per cent dextrose in water was slowly infused intravenously when a steady state was assured initial control measurements were made while the subject was supine Afterward another solution containing 0 4 micrograms per milliliter of isoproterenol was administered at a rate of from 50 to 120 drops per minute (02 to 04 μg Kg /min) Facial flushing hyperventilation precordial pounding or occasional tremulousness occurred in a few subjects within a minute or two and usually were accompanied by tachycardia and increased arterial pulse pressure After 4 to 7 minutes when a steady state was apparent by inspection of the spirogram and recordings of arterial pressure samples of blood were drawn for determination of oxygen content As judged by inspection of the heart rate and pulse pressure the effects of isoproterenol disappeared within 5 minutes after the infusion was stopped Under these conditions there were no adverse clinical effects with this drug

After 25 to 40 minutes additional control observations were made in 9 patients after they had been sitting in a chair for several minutes Then each subject walked on a treadmill at a rate of 1 7 miles per hour at a 10 per cent grade of incline After 4 minutes of steady state exercise samples of blood were withdrawn and ventilation and oxygen consumption were recorded for another determination of cardiac output

In five instances the subjects were exercised first and the observations with isoproterenol were made several minutes later with no discernible difference in results due to this change in experimental procedure

When the subjects were supine the zero reference was placed at 10 cm above the table when they were upright it was reset at the level of the fourth rib anteriorly Arterial pressures were integrated planimetrically or electrically total pulmonary and systemic resistance indices were computed by formula 1 (top of page) Apparent left ventricular work was estimated by formula 2 (top of page) where 1 065 = specific gravity of whole blood P_{SA} = mean systemic arterial pressure and 13 6 = specific gravity of mercury Apparent stroke work of the left ventricle was derived by dividing the foregoing value by the heart rate

All data were processed in an IBM 650 digital computer to derive means standard deviations and 1 080 cross correlations by the product moment method

Results

A statistical analysis of the mean responses of two types of patients with left heart diseases to three different experimental procedures is presented in Table I The salient differences between these two types of patients as well as the significant changes common to both are listed in Table II Average responses of the components of cardiac output to the stress of exercise in the upright position are shown in Fig 1

I Hemodynamic observations in patients resting in the supine position The 7 patients with left ventricular diseases had virtually normal pressure and flow measurements while resting in the recumbent position except for 1 individual with a slight elevation of the wedged pulmonary arterial

Isuprel Winthrop-Stearns

Calculations of left ventricular work for the patients with aortic valvular disease were not based upon the actual pressure within the left ventricle similarly the volume of regurgitant flow was not determined

(PC) pressure. Hence none of the other 6 patients had significant evidence of left ventricular failure by these criteria.

All patients with mitral stenosis had a moderate but definite increase in PC pressure. Ventilation, pulmonary arterial pressure and total pulmonary resistance tended to be higher, just as the cardiac and stroke indices tended to be lower in patients with mitral stenosis than in patients with left ventricular diseases. These differences were not significant ($p > .05$) because of appreciable variation for the small number of patients involved in this study. However, ventilation varied inversely with stroke index ($r = -0.94$) and directly with total pulmonary resistance ($r = +0.95$) in mitral stenosis but not in those with left ventricular diseases ($r = -0.14$ and -0.10, respectively). The lower arterial oxygen content in the patients with mitral stenosis was related to a lower hemoglobin concentration.

II. Effects of isoproterenol in patients in the supine position. Intravenous infusion of isoproterenol produced hyperkinemia, systemic vasodilatation and mild hyperventilation in both types of patients. The high output state was achieved primarily by acceleration of heart rate. Since the increased cardiac index was in excess of metabolic demands for oxygen consumption, the arteriovenous oxygen difference diminished. Despite the fall in systemic resistance, the apparent work of the left ventricle was increased, largely as a result of the moderate tachycardia.

All patients with left ventricular diseases and 5 of the 7 with mitral stenosis showed a fall in total pulmonary resistance. Patients with mitral stenosis showed a greater increase in oxygen consumption, presumably reflecting increased work of the right ventricle against augmented pulmonary arterial pressure as well as the increased work of breathing. In the two instances in which changes in PC pressure were observed in patients with mitral stenosis, it increased from 23 to 28 and from 24 to 45 mm Hg in response to isoproterenol.

III. Effects of sitting upright. Both types of patients showed a significant fall in stroke index. Since the heart rate accelerated slightly, this prevented a corresponding fall in cardiac index. Nevertheless, arteriovenous oxygen difference widened and oxygen consumption increased slightly. Presumably these changes reflected an alteration in the distribution of the blood volume imposed by the change in the position of the body with respect to gravitational force and a slight increase in metabolic activity of the muscles maintaining this posture. Despite the probable reduction of blood volume in the thorax, mean pulmonary arterial pressure increased slightly. Possibly the latter change represented an error in estimation of the zero reference level under these conditions. There were then no significant changes with posture unique to either type of patient, but the arteriovenous oxygen difference varied inversely with the cardiac index ($r = -.92$) only in patients with left ventricular diseases (vs. $r = -.21$ in those with mitral stenosis).

IV. Effects of exercise on patients in the upright position. Both types of patients exhibited marked increases in oxygen consumption and ventilation as a result of the enhanced metabolic activity in the exercising skeletal muscles. The augmented oxygen transport was achieved by a substantial increase in both cardiac index and arteriovenous oxygen difference. The former resulted primarily from an acceleration of heart rate. Apparent left ventricular work was raised accordingly, although a slight increase in stroke work was contributory in patients with left ventricular diseases. The fall in systemic resistance probably represented vasodilation accom-



Fig. 1. Cardiac adaptations to exercise in upright position in terms of average changes in stroke index and heart rate, as compared with sitting at rest in normal subjects and patients with either left ventricular diseases or mitral stenosis. (See text for details.)

Table I. Mean values ± standard deviations

	Left ventricular disease (N = 7)				Mitral disease (N = 7)			
	Supine	L. l. exercise	Sitting	Walking	Supine	L. l. exercise	Sitting	Walking
Ventilation (L./min.)	8.0 ± 1.6	13.3 ± 1.5	9.9 ± 1.9	25 ± 5.2†††	10.6 ± 6.5	17.8 ± 5.9	13.3 ± 7.1	31.7 ± 10.1††††
Oxygen consumption (ml./M.²/min.)	132.6 ± 16.3	137.5 ± 59.6	155.5 ± 11.2	509.1 ± 66.5†††	115.6 ± 27.5	177.3 ± 15.0*	139.7 ± 29.9	101.1 ± 138.3††††
Arterial O₂ content (vol. %)	19.9 ± 1.9	19.8 ± 1.2	20.1 ± 1.8	20.5 ± 1.5	17.9 ± 1.5	19.2 ± 1.6	18.3 ± 1.2	18.9 ± 1.2
Mixed venous O₂ content (vol. %)	15.1 ± 2.5	16.5 ± 2.2	13.6 ± 1.6	9.3 ± 3.3†††	12.9 ± 1.5	13.6 ± 2.1	12.2 ± 0.9	7.3 ± 0.7†††
A-V O₂ difference (ml./L.)	49.1 ± 13.7	33.6 ± 6.5	66.6 ± 11.2	112.3 ± 19.0†††	49.2 ± 10.5	55.6 ± 10.6	60.5 ± 7.4	115.9 ± 12.7†††
Cardiac index (L./M.²/min.)	3.0 ± 1.0	5.0 ± 1.3	2.5 ± 0.9	4.7 ± 0.9†††	2.5 ± 0.7	3.2 ± 1.5	2.3 ± 0.5	3.5 ± 1.4†
Heart rate	66.4 ± 11.9	91.0 ± 27.6	72 ± 12.0	115.5 ± 31.3†††	73.4 ± 19.0	111.6 ± 4.1	95.6 ± 23.5	137.7 ± 28.9†††
Stroke index (ml./M.²)	46.0 ± 13.7	55.0 ± 16.9	31.8 ± 7.5	41.5 ± 13.7	34.0 ± 9.7	31.0 ± 22.4	25.0 ± 5.7	27.7 ± 11.7
Mean P.A. pressure (mm. Hg)	15.9 ± 3.5	16.5 ± 12.3	20.5 ± 3.2	29.3 ± 4.1†††	29.9 ± 7.5	33.3 ± 22.1	32.1 ± 10.1	37.7 ± 20.2
Mean brachial artery pressure (mm. Hg)	100.9 ± 13.3	90.0 ± 20.4	116.6 ± 15.1	121.3 ± 16.5	96.3 ± 12.1	101.0 ± 19.2	114.0 ± 23.0	113.1 ± 25.9
Total pulmonary resistance (dynes sec. cm.⁻⁵ M.²)	517 ± 2	0 ± 133**	718 ± 256	510 ± 200	1,063 ± 153	916 ± 762	1,216 ± 613	1,216 ± 634
Systemic resistance (dynes sec. cm.⁻⁵ M.²)	3,014 ± 1,034	1,231 ± 535	1,057 ± 1,250	2,177 ± 151	3,386 ± 1,221	2,259 ± 1,207	1,179 ± 1,299	3,027 ± 1,597
L.V. work (Kg. M./min./M.²)	1.12 ± 1.16	6.35 ± 2.19	1.97 ± 0.55	5.11 ± 2.39†††	3.30 ± 0.91	5.92 ± 2.73	3.63 ± 0.92	5.15 ± 2.15
L.V. stroke work (Kg. M./beat/M.²)	.065 ± .0.3	0.4 ± .035	.052 ± .016	.072 ± .019	.047 ± .011	.062 ± .037	.046 ± .070	.041 ± .0.3

Probabilities (P) of differences from supine ... being <.05 * <.01 ** <.001 [illegible]
†Probability (P) of change from sitting to walking being <.05 †† <.01 ††† <.001
‡Stroke work per ... per minute ... [illegible]

Table II. Average magnitude of significant differences with type of disease and changes with experimental procedures ($p < .05$)

Type of left heart disease	Experimental procedure	Number of observations	Variable	Average difference or change	Average difference or change %	p
Mitral stenosis (... vs. ...)	Supine control	7	Mean LA pressure	+11 mm Hg	55	< .001
	Supine control	7	Arterial O_2 content	−2.0 vol	− 10	< .01
Left ventricular disease	Isoproterenol (... supine)		Total pulmonary resistance	−277 dynes ... cm ... M	− 51	< .001
		7	Systemic resistance	−1,590 dynes sec cm ... M	− 62	< .001
		7	Ventilation	+5.3 L/min	+ 66	< .01
		7	AV O_2 difference	−14.8 ml/L	− 31	< .0
	Exercise (sitting upright)	7	LV work (apparent)	+4.01 kg M/min/M	+10	< .001
		7	Systemic resistance	−1,880 dynes ... cm ... M	− 46	< .001
		7	Mean LA pressure	+9 mm Hg	+ 41	< .001
Mitral stenosis	Isoproterenol (... lying supine)	7	Oxygen consumption	+59 ml/M/min	+ 50	< .01
Both types	Sitting upright (vs. lying supine)	14	Stroke index	−11 ml/M	− 27	< .001
		14	AV O_2 difference	+14.9 ml/L	+ 31	< .001
		14	Mean LA pressure	+... mm Hg	+ 17	< .02
		14	Oxygen consumption	+ ... ml/M/min	+ 17	< .03
	Isoproterenol (... lying supine)	14	Cardiac index	+1.87 L/M/min	+ 69	< .001
		14	Systemic resistance	−1,460 dynes sec cm ... M	− 45	< .001
		14	Heart rate	+31	+ 49	< .00
		14	LV work (apparent)	+2.4 kg M/min/M	+ 63	< .001
		14	Mixed venous O_2 content	+2.15 vol	+ 15	< .01
		14	AV O_2 difference	−9.16 ml/L	− 19	< .03
		14	Ventilation	+6.2 L/min	+ 65	< .07
	Exercise (sitting upright)	14	Oxygen consumption	+308 ml/M/min	+210	< .001
		14	Ventilation	+16.8 L/min	+145	< .001
		14	AV O_2 difference	+30.4 ml/L	+ 9	< .001
		14	Mixed venous O_2 content	−4.55 vol	− 35	< .001
		14	LV work (apparent)	+2.98 kg M/min/M	+ 78	< .001
		14	Cardiac index	+1.72 L/min/M	+ 72	< .001
		14	Heart rate	+34	+ 53	< .001
		14	Systemic resistance	−1,370 dynes sec cm ... M	− 37	< .002
		14	Mean LA pressure	+12 mm Hg	+ 46	< .03

panying the increased flow Mean pulmonary arterial pressure rose somewhat especially in patients with mitral stenosis Radial arterial pressure was not significantly altered in either group but tended to rise in those with left ventricular diseases and to fall in the individuals with mitral stenosis

Discussion

Both normal subjects and cardiac patients exhibit a fall in stroke volume and cardiac output when they change from the supine position to sitting upright Inasmuch as estimates of the central blood volume have revealed a corresponding decrease with this change in posture[10] it is likely that there was a proportionate reduction in atrial volumes and in turn the diastolic filling volumes of the ventricles Thus these changes in blood flow with changes in posture are compatible with the Starling hypothesis that the amount put out at each beat depends directly on the diastolic filling [11]

Myocardial stimulation with isoproterenol produced more acceleration of heart rate in the cardiac than in the normal subjects[1] Indeed in patients with mitral stenosis there was an even greater positive chronotropic response as well as a smaller positive inotropic response in stroke index Statistically normal subjects were reported[16] to increase stroke index significantly (p < 02) but neither type of cardiac patient reported here showed a significant increase (p > 1) This response undoubtedly varies with the quantity of drug administered and with the selection of cardiac patients made for previous studies[17] on patients with left ventricular diseases have demonstrated a small rise in stroke index with isoproterenol (p < 03) Because of the faster heart rate in cardiac patients reported here changes in left ventricular work per minute and systemic resistance during infusion with isoproterenol were similar to those observed in normal subjects

Total pulmonary resistance diminished during infusions of isoproterenol in patients with left ventricular diseases In a few instances in which changes in PC pressure were measured there was a decrease in these patients in contrast to a rise in those with mitral stenosis in whom the stenotic lesion produced a relatively fixed resistance to filling of the left ventricle Hence the increased pulmonary capillary pressure was a result of increased flow through a small mitral orifice Ventilation in patients with mitral stenosis also tended to be higher with isoproterenol than in patients with left ventricular diseases It should be noted however that in the making of these comparisons with left ventricular diseases the observations were based upon patients who did not exhibit pulmonary hypertension secondary to left ventricular failure

Exercise in the upright posture produced the expected increase in oxygen consumption and rise in ventilation heart rate cardiac index and left ventricular work as well as widening of the arteriovenous oxygen difference Systemic resistance diminished as blood flow increased In contrast to the findings in normal subjects stroke index showed only a small average increase above the resting value when the subjects were seated (Fig 1) Despite greater acceleration of heart rate cardiac index did not increase as much in these cardiac patients as in normal subjects performing a comparable amount of work on the treadmill

Patients with mitral stenosis differed from those with left ventricular diseases in their responses to exercise in that the average stroke volume did not increase above the resting value while they were seated Also in the patients with mitral stenosis mean systemic arterial pressure failed to increase This phenomenon of exertional hypotension was described previously in association with the inability to increase stroke index with exertion above the level found in the upright posture at rest Thus the capacity to increase the effective stroke output with exertion was quantitatively more impaired in patients with mitral stenosis who had high resistance to diastolic filling of the left ventricle The other components of oxygen transport namely heart rate and arteriovenous oxygen difference were not limited but rather tended to exhibit compensatory increases above the normal range With exercise however pulmonary arterial pressure increased in all instances whereas total pulmonary resistance exhibited a

wide range of responses Since the PC pressure was not recorded under this experimental condition no inference could be made with regard to changes in vascular resistance

Ventilation increased in response to isoproterenol This was a significant change in patients with left ventricular diseases and not associated with any rise in pulmonary arterial pressure In patients with mitral stenosis who also had some pulmonary vascular engorgement increases in ventilation were correlated with a rise in pulmonary arterial pressure under all experimental circumstances (r ranged from +0 68 to +0 85) Whereas the ventilatory response could be mediated primarily by central neurogenic mechanisms it was possibly enhanced by stimulation of pulmonary stretch reflexes in patients with mitral stenosis

Cardiac index was correlated with oxygen consumption in all 14 patients (r varied from +0 54 during isoproterenol to +0 86 during walking) Hence regulation of cardiac output was determined largely by metabolic activity as reflected in the total body oxygen consumption Undoubtedly it was modified in accord with Starling's concepts by the effects of changes on the distribution of blood volume available for diastolic filling of the ventricles Under special circumstances it was predominantly affected by myocardial stimulation Finally in these patients with cardiovascular diseases regulation was altered by pathologic mechanisms affecting diastolic filling and effective systolic ejection of the left ventricle Although stroke index correlated with cardiac index (r ranged from +0 68 to +0 90) heart rate was not related to cardiac index during recumbency isoproterenol or sitting (r = −0 39 to +0 07) but was inversely related during walking (r = −0 59) This lack of a direct relationship is attributed to the excessive increase in heart rate as a compensatory mechanism for approaching a more nearly adequate cardiac output relative to the metabolic requirements of the body Thus when the capacity to increase stroke index is impaired by disease a relative tachycardia is the only compensatory response available to the heart If the available acceleration of heart rate is insufficient to produce the necessary flow of blood to meet the metabolic requirements of the peripheral tissues further increases in arteriovenous oxygen difference or rate of oxygen extraction from the available blood flow ensue Failure of these mechanisms initiates a compensatory increase in anaerobic metabolism at the cellular level [3]

Summary

1 Cardiovascular responses to changes in posture exercise in the upright position and myocardial stimulation with isoproterenol have been studied in 14 patients with diseases of the left side of the heart Seven patients had limitations of diastolic filling of the left ventricle imposed by mitral stenosis and 7 patients had lesions which reduced the effective systolic ejection of the left ventricle

2 In both types of patients stroke index fell and arteriovenous oxygen difference widened significantly with a change in posture from supine to sitting upright

3 The mean values during rest in the recumbent position were virtually normal for patients with left ventricular diseases Although heart rate and cardiac index increased significantly with the exertion of walking stroke index increased toward but not above the resting supine value and the mean arterial pressure on the average increased slightly

4 Patients with mitral stenosis tended to have lower stroke and cardiac indices and higher pulmonary arterial pressure and ventilation during rest in the recumbent position Cardiac index was increased by the exertion of walking largely because of a disproportionate acceleration of heart rate stroke index on the average showed no increase above the lowered value produced by the patient's sitting upright The average systemic arterial pressure for these patients did not rise

5 Myocardial stimulation with isoproterenol during recumbency significantly increased heart rate cardiac index and left ventricular work and lowered systemic arterial resistance in both types of patients Except in 2 patients with pulmonary vascular disease total pulmonary resistance diminished

6 A primary defect of patients with diseases of the left side of the heart is an

impaired capacity to increase stroke output in response to exertion or to myocardial stimulation This may result from a number of mechanisms distorting effective systolic ejection Such capacity is particularly restricted by lesions such as mitral stenosis that offer increased resistance to diastolic filling of the left ventricle Compensatory mechanisms include tachycardia widening of the arteriovenous oxygen difference and anaerobic metabolism

7 There was a significant correlation in patients with mitral stenosis between minute ventilation and pulmonary arterial pressure under each experimental state

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REFERENCES

1 Bruce R A Cobb L A Katsura S Morledge J H Andrus W W and Fuller J F Exertional hypotension in cardiac patients Circulation 19 533 1959
2 McMichael J and Sharpey Schafer E P Cardiac output in man by direct Fick method Effects of posture venous pressure change atropine and adrenalin Brit Heart J 6 33 1944
3 Nowy on H Kikodi K and Zollner N Vergleichende Messungen des zentralen Blutvolumen und bestimmten Volumens in Liegen und in Stehen Ztschr Kreislaufforsch 46 393 1957
4 Rushmer R F Postural effects on the baselines of ventricular performance Circulation 20 897 1959
5 Rushmer R F Constancy of stroke volume in ventricular responses to exertion Am J Physiol 196 745 1959
6 Musshoff K Reindell H and Klepzig H Stroke volume arteriovenous difference cardiac output and physical working capacity and their relationship to heart volume Acta cardiol 14 427 1959
7 Mitchell J H Sproule B J and Chapman C B The physiological meaning of the maximal oxygen intake test J Clin Invest 37 538 1958
8 Kao F F and Ray L H Regulation of cardiac output in anesthetized dogs during induced muscular work Am J Physiol 179 255 1954
9 Gray I and Beetham W P J Changes in plasma concentration of epinephrine and norepinephrine with muscular work Proc Soc Exper Biol & Med 96 636 1957
10 Lands A M and Howard J W A comparative study of the effect of l arterenol epinephrine and isopropylarterenol on the heart J Pharmacol & Exper Therap 106 65 1952
11 Nathanson M H and Miller H Effect of 1 (3 4 dihydroxyphenyl) 2 isopropylamino ethanol (isopropylepinephrine) on the rhythmic property of the human heart Proc Soc Exper Biol & Med 70 633 1949
12 Rushmer R F and West T C Role of autonomic hormones on left ventricular performance continuously analyzed by electronic computers Circulation Res 5 240 1957
13 Winterscheid L C Bruce R A Blumberg J B Leyse R M and Merendino K A Effects of isoproterenol on carbohydrate metabolism of the isolated canine heart Unpublished observations 1960
14 Dodge H T and Murdaugh H V Drug driving of the heart in man (abstract) J Clin Invest 36 883 1957
15 Wessler A M Leonard J J and Warren J V The hemodynamic effects of isoproterenol in man J Lab & Clin Med 53 921 1959
16 Eckstein J W and Hamilton W K Effects of isoproterenol on peripheral venous tone and transmural right atrial pressure in man J Clin Invest 38 342 1959
17 Bruce R A Cobb L A Katsura S and Morledge J Comparative hemodynamic effects of isoproterenol and exercise (walking) in cardiac patients (abstract) J Clin Invest 37 881 1958
18 Chappel C I Rona G Blatt T and Gaudry R Comparison of cardiotoxic actions of certain sympathomimetic amines Canad J Biochem & Physiol 37 35 1959
19 Bruce R A Evaluation of functional capacity and exercise tolerance of cardiac patients Mod Concepts Cardiovas Dis 25 321 1956
20 Warren J V and Wessler A M Central blood volume as a factor in the regulation of the circulation (abstract) Circulation 18 793 1958
21 Patterson S W and Starling E H On the mechanical factors which determine the output of the ventricles J Physiol 48 357 1914
22 Cobb L A Johnson W P and Bruce R A Responses in stroke volume to upright exercise in man Clin Res 9 84 1961
23 Huckabee W E and Judson W E The role of anaerobic metabolism in the performance of mild muscular work I Relationship to oxygen consumption and cardiac output and the effect of congestive heart failure J Clin Invest 37 1593 1958

The value of the apexcardiogram as a reference tracing in phonocardiography

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The growing importance of phonocardiography as a diagnostic tool has emphasized the need for a simpler and better reference tracing. Indirect arterial tracings[1] carotid and peripheral (femoral, brachial, and radial) are of aid in identifying the aortic and pulmonic components of the second sound, but they are of no value in the identification of the diastolic events of the cardiac cycle. The jugular venous tracing is the best reference tracing available to identify the events from the right side of the heart, as has been recently emphasized by Hartman.[2] The time lag from the right auricle to the jugular vein, with the present type of recording devices, seems to be negligible. However, only indirectly does the jugular venous pulse give information of the events in the left side of the heart.[2]

Since 1957, we have been recording the movements of the chest wall overlying the left and right ventricles and designating the tracings as the apexcardiogram (ACG). With careful attention to detail and in certain specific conditions, the activity of the two ventricles can be separated, the right and left apexcardiogram. Hartman[2] prior to this time had established the value of this measurement.

Material and method

The present report is based on our experience with over 1,200 patients in whom the ACG was recorded. In over 200 patients the ACG was obtained before and after heart operation for correction of various congenital and acquired malformations of the left and right sides of the heart.

In the great majority of our patients the clinical diagnosis was confirmed by right or left heart catheterization, cineangiocardiography, and dye dilution studies, as well as operation or postmortem examination. All the tracings in this report were recorded from patients with diagnoses proved by cardiac catheterization or operation.

The equipment used for recording the phonocardiograms and apexcardiograms was the Sanborn Twin Beam phonocardiograph with a Sanborn microphone (62-1500 C 13). The paper speed was 75 mm. per second. The ACG was recorded using a pulse crystal microphone (Sanborn 4374) which reproduces an electrical signal proportional to changes in pressure in the tubing. Frequency response of this crystal microphone is from 1 to 1,000 cycles per second. Detailed study of the electronic characteristics of this system has been

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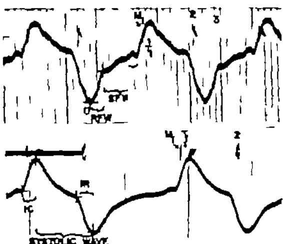


Fig 1 Apexcardiogram of the left ventricle Normal subject Split first sound in both tracings occurring before the peak of the systolic wave Components of the apexcardiogram described in the text IC Isometric contraction IR Isometric relaxation RFW Rapid filling wave SFW Slow filling wave a Atrial

escribed by Miller and White After ompletion of the routine PCG the point f maximal impulse with the patient in the ft lateral decubitus position was deter n ned by palpation and a left ventricular omplex was confirmed on the electrocar logram from this point The sound micro hone was then positioned so that the ack up bell with side opening tube was placed directly over the point of maximal mpulse and the ACG was recorded simul aneously with the ECG When it was lesirable to have the microphone at a dif erent auscultatory area that was not the apex a funnel type of cup applicator (as used to record the indirect carotid tracing) was used The tracings were recorded in mid-expiration The technique to record the right ventricular ACG was essentially the same as described above except that the pick up bell or the cup applicator was placed at the left sternal border fourth or fifth intercostal space and a right ventricu lar electrocardiographic complex was re corded from this area

The following abbreviations have been employed in this report 1 first sound 2 second sound 3 third sound 4 fourth sound A aortic valve closure P pul monic valve closure OS opening snap SM systolic murmur DM diastolic mur mur ASM atrial systolic murmur ACG apexcardiogram O point beginning of filling wave RFW rapid filling wave SFW slow filling wave IC isometric con traction IR isometric relaxation a atrial wave Vertical lines in the tracings are 0 04 second apart In several patients the ACG was recorded during right or left heart catheterization with simultaneous atrial and ventricular pressure curves In these circumstances the ACG was recorded with the Sanborn Poly Viso

*The term ... is ... used to describe the tracing recorded at ... which represents the movement of the body ... rather than the ... However the terminology is ... known and ... have used it simply because it has been ... d and is generally ... d

Normal apexcardiogram

A normal ACG presents the following waves *a waves* due to atrial contraction *systolic wave* due to ventricular contrac tion *rapid filling wave* (*RFW*) due to rapid early diastolic filling *slow filling wave* (*SFW*) follows the RFW and ends at the level of the a wave representing the slow ventricular filling (see Fig 1)

After the atrial contraction represented by an a wave which is coincident with

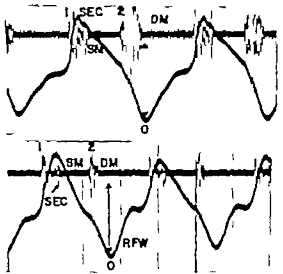


Fig 2 Apexcardiogram of the right ventricle Two cases of ventricular septal defect with severe pulmonary hypertension Note the presence of systolic eject on click which follows the peak of the systolic wave by 0 03 to 0 04 second Observe the diastolic murmur of pulmonary insufficiency starting before the O point The phonocardiogram were recorded at the left sternal border fourth intercostal space with logarithmic technique Compare with Fig 1

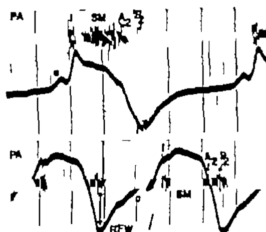


Fig 3 Apexcardiogram of the right ventricle *Top* Pulmonary stenosis and ventricular septal defect *Bottom* Atrial septal defect Note the widely split second sound with both components preceding the O point Small ves are recorded in both tracings Systolic ejection murmur Compare with Fig 4

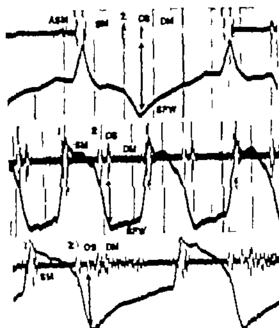


Fig 4 Apexcardiogram of the left ventricle Mitral stenosis Note the opening snap of the mitral valve consistently coincident with the O point Observe absence of rapid filling wave Phonocardiographic signs of mitral stenosis Mid diastolic murmur starting after the beginning of SFW In the top tracing the opening snap could be confused with third sound because of the long 2 OS interval (0 11 second) Compare with Fig 11 The phonocardiograms were recorded at the apex

the fourth sound the tracing reveals a rapid rise reaching a maximal peak at the moment of the closure of the atrioventricular valves That component (from the end of the a wave to the peak of the systolic wave) appears to represent the isometric contraction

The systolic wave has usually a tent shape followed by a systolic depression which reaches at that level a plateau and finally a sharp and rapid drop at the end of the systole At that moment the tracing reaches the base line and this point marks the opening of the A V valves and the beginning of the diastolic filling phase of the ventricles (O point) The second sound precedes the beginning of the filling wave by 0 04 to 0 08 second (Fig 1)

The early diastolic filling is represented in the ACG by a sharp rise which reaches a definite peak this peak being coincident with a third sound The duration of the RFW ranges from 0 04 to 0 12 second depending on the total diastolic period of the cardiac cycle This RFW represents in height 10 to 30% of the total amplitude of the tracing (100 per cent) From that point the RFW is substituted by a slow rising which represents the slow filling wave The slow filling wave ends at the level of the a wave and represents the end of passive diastolic filling (Fig 1)

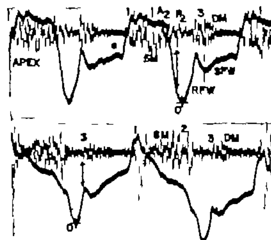


Fig 5 Apexcardiogram of the left ventricle Mitral regurgitation Note the third sound and short diastolic murmur starting at the peak of the rapid filling wave which is very prominent In the top tracing note the split of the second sound The pulmonic component of the second sound should not be confused with the opening snap since it occurs before the O point Compare with Fig 4

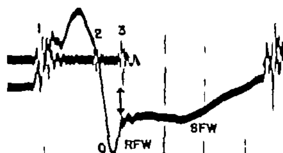


Fig 6 Apexcardiogram of the right ventricle Constrictive pericarditis Note a prominent third sound coincident with the peak of rapid filling wave

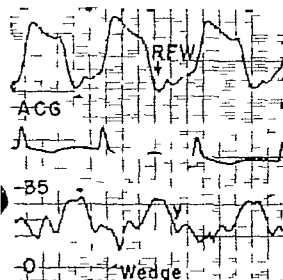


Fig 7 Simultaneous recording of the left ventricular apexcardiogram electrocardiogram and pulmonary wedge tracings in a patient with mitral regurgitation Note the beginning of RFW (O point) coincident with the peak of the wave (opening of the mitral valve)

Time relationship of the events in the cardiac cycle as related to the apexcardiogram

1 First sound The first sound usually precedes the peak of the systolic wave by an average of 0 02 second In conditions associated with splitting of the first sound both components should precede the peak of the systolic wave The ACG seems to be of important value in this particular instance since it is possible to differentiate the split of the first sound from the systolic ejection click (Figs 1 and 2) However it should be mentioned that occasionally due to very short isometric contraction as occurs in cases of severe right or left ventricular hypertension the systolic ejection click will occur very early in systole and will be almost inscribed with the first sound making the separation between the two components nearly impossible by any method[1,8]

2 Systolic ejection click The systolic ejection click follows the peak of the systolic wave by 0 04 to 0 08 second[1] The differentiation from split first sound was discussed above (Fig 2)

3 Mid systolic click The mid systolic click usually coincides with the initial descending limb of the systolic wave and is often coincident with the systolic plateau

4 Second sound The ACG is of special value in differentiating the second sound from the opening snap[7] However it does not separate the two components of the second sound (A_2 and P_2) and in this particular instance the carotid tracing is a superior reference tracing Nevertheless both components of the second sound precede the beginning of the filling wave and *the differential diagnosis between* opening snap and split second sound is based on this fact (Figs 3 and 4)

5 Opening snap The ACG is extremely useful in the identification of the opening

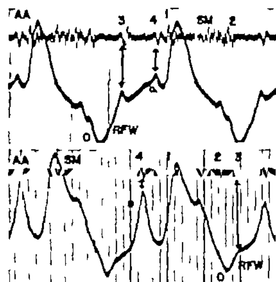


Fig 8 Apexcardiogram of the left ventricle Two cases of aortic stenosis Quadruple rhythm with third sound coincident with the peak of RFW and fourth sound with wave Note giant wave in the bottom tracing suggesting powerful left atrial contraction Observe also that the ejection murmur starts after the peak of the systolic wave



Fig 9 Apexcardiogram of the right ventricle. Severe isolated pulmonary valvular stenosis. Systolic ejection murmur starting after the peak of the systolic wave. Note the fourth sound coincident with the peak of a in the apexcardiogram



Fig 10 Apexcardiogram of the left ventricle. Arteriosclerotic heart disease with left heart failure. Note fast heart rate (115 per minute) third sound gallop coincident with rapid filling wave (*RFW*) and atrial systolic murmur (*ASM*) coincident with prominent

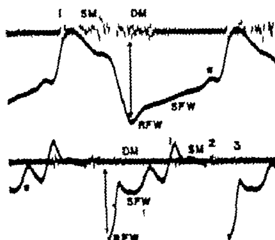


Fig 11 Apexcardiogram of the left ventricle. Top P tent ductus arteriosus without pulmonary hyper tension. Note continuous murmur going through the second sound. The diastolic component of this murmur starts before the O point in the ACG. *Bottom* Aortic regurgitation. Observe the arterial diastolic murmur starting before the O point which is very prominent T II es Compare with Fig 4

snap of the mitral or tricuspid valve The opening snap should always be coincident with the beginning of the filling wave (O point) Since the ACG records the movement of the chest wall overlying the ventricle the time delay due to pulse wave transmission is negligible (Fig 4)

6 *Third sound* The third sound when present is coincident with the peak of the rapid filling wave which marks the end of rapid diastolic filling (Figs 5 and 6) Simultaneous left ventricular ACG with pulmonary wedge or left atrial curves demonstrates that the beginning of the RFW (O point) is coincident with the v descent of the v wave (which marks the opening of the A V valve) and the end of the RFW is coincident with the end of the y descent which marks the end of rapid emptying of the right or left atrium (Fig 7)

7 *Fourth sound* The ACG can be used to identify the fourth sound The fourth sound which is due to atrial contraction produces an a wave in the ACG Conditions associated with right or left auricular overload exaggerate the a wave of the ACG The fourth sound should be coincident with the a wave of the ACG

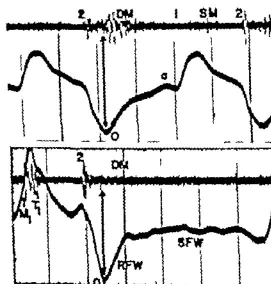


Fig 12 Apexcardiogram of the right ventricle *Top* Moderately severe pulmonary regurgitation after pulmonary valvulotomy for correction of pulmonary stenosis. Note that the diastolic murmur precedes the O point. *Bottom* Pulmonary regurgitation in patient with primary pulmonary hypertension (RV pressure of 130/5 mm Hg) In addition to the diastolic murmur which starts before the O-point note the split of the first sound with both components preceding the peak of the systolic wave

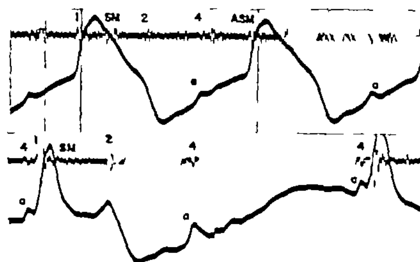


Fig 13 Apexcardiogram of the left ventricle *Top* Aortic stenosis and insufficiency with first-degree A V block Note the time interval between the atrial wave and the systolic wave (0 29 second) *Bottom* Arteriosclerotic heart disease with 2 1 block Note the a wave coincident with the fourth sound These arrhythmias were confirmed by the electrocardiogram

(Figs 8 and 9) Simultaneous ACG with atrial curves demonstrates that atrial and apexcardiographic a waves occur simultaneously

8 *Systolic regurgitant murmurs* The ACG identifies a systolic regurgitant murmur perhaps better than does the carotid tracing in so far as time relationship is concerned Mitral or tricuspid regurgitation and ventricular septal defects produce murmurs which start immediately after the first sound When the heart murmur is recorded simultaneously with the ACG it is noted that the murmur starts immediately after the peak of the systolic wave (Fig 5)

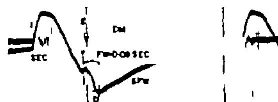


Fig 14 Apexcardiogram of the left ventricle Mitral stenosis Note the systolic ejection click occurring after the peak of the systolic wave Observe the absence of the opening snap Nevertheless the distance between the second sound and the opening of the mitral valve can be calculated by measuring the time interval between the second sound and the beginning of the filling wave (2 FW interval) Note also the absence of a rapid filling wave

9 *Systolic ejection murmurs* Aortic stenosis pulmonic stenosis and murmurs due to increased flow across the pulmonic or aortic valves produce a typical murmur which starts somewhat late in systole and ends before the second sound These murmurs when timed against the ACG start after the peak of the systolic wave having maximal intensity during the first descending limb of the systolic wave which represent the period of maximal ventricular ejection (flow at high velocity) (Figs 3 and 9)

10 *Atrial systolic murmurs* Mitral stenosis and tricuspid stenosis with sinus rhythm septal defects heart failure etc. produce an atrial systolic murmur which starts with the a wave of the ACG and ends at the following isometric contraction just prior to the peak of the systolic wave as demonstrated in Figs 4 and 10

11 *Atrioventricular diastolic murmur* The ACG is of special value in differentiating an atrioventricular murmur from an arterial diastolic murmur In the former the murmur starts at the beginning of the filling wave in the ACG and in the latter the murmur starts prior to the filling wave (Figs 4 and 5)

12 *Arterial diastolic murmurs* Aortic and pulmonary insufficiency produce a diastolic murmur that starts during iso-

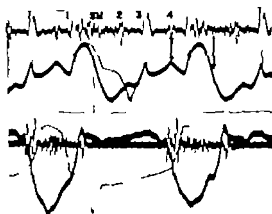


Fig 1 Artefacts in the apexcardiogram *Top* Somewhat common type of artefact Note that there is marked drop in the systolic wave (*arrow*) with a small positive wave at the level of the second sound The late part of the rapid filling wave is well recorded and is coincident with the third sound The wave holds normal relationship to the fourth sound The expected configuration of the apexcardiogram is indicated by the dashed line *Bottom* Apexcardiogram of the right ventricle demonstrating artefactual rapid filling wave Note the systolic drop of the systolic wave The two components of the second sound were identified in other tracings by the relationship to the dicrotic notch of the carotid tracing



Fig 16 Common type of artefact occurring when the pulse was picked up placed on the periphery rather than exactly over the apex beat Thus an out-of phase pulse is recorded and registers negative systolic deflection The expected configuration of the apexcardiogram is indicated by the dashed line

metric relaxation of the left or right ventricle consequently before the atrioventricular valves open (Figs 11 and 12) In that circumstance the ACG readily identifies the type of murmur by its relationship to the diastolic filling wave as described above

13 Arrhythmias The apexcardiogram seems to be a useful aid in the identification of certain types of arrhythmias and atrioventricular conduction effects As demonstrated in Fig 13 a first-degree A V block is readily identified by prolongation of the interval between the a wave and the beginning of the systolic wave

Right ventricular apexcardiogram By means of this technique the right ventricular ACG was very seldom recorded in a normal subject In a few cases in which tracings were obtained at the left sternal border third to fifth intercostal space no reproducibility was obtained Perhaps a more sensitive type of device requiring a more complex type of equipment as described by Eddleman[11,12] and Harrison[13] would allow a more nearly accurate tracing However in conditions associated with right ventricular overload a right ventricular ACG can be recorded and presents the same components as described above for the ACG of the left ventricle (Figs 2 3 6 9 and 12) Occasionally as was emphasized by Hartman[8] one may be able to record an ACG from the right and left ventricles in the same patient

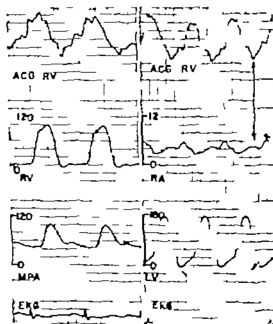


Fig 17 Simultaneous right ventricular apexcardiogram with electrocardiogram and pressure curves of the right ventricle (*RV*) main pulmonary artery (*MPA*) right atrium (*RA*) and left ventricle (*LV*) Note a wave of the ACG coincident with waves in the right atrial curves and P waves in the EKG Observe also the beginning of ejection in the MPA curves coincident with the peak of the systolic wave in the ACG

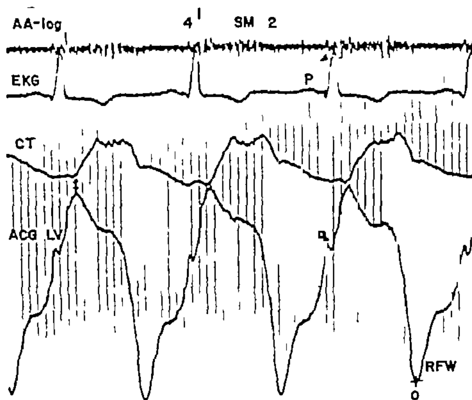


Fig 18 Simultaneous left ventricular pericardiogram (*ACG LV*) indirect carotid tracing (*CT*) electrocardiogram (*EKG*) and phonocardiogram in patient with aortic stenosis Note that the fourth sound occurs at the peak of a wave Observe also the beginning of ejection in the carotid tracing coincident with the peak of the systolic wave in the ACG The dicrotic notch of the CT precedes the O-point in the ACG by 0 03 second

Discussion

The ACG seems to fulfill almost all requirements of an ideal reference tracing in phonocardiography It does not provide information about the two components of the second sound although it differentiates the second sound from the opening snap of the mitral valve as demonstrated in Figs 3 4 and 5 It is by far superior to the carotid tracing electrocardiogram and in many instances it does obviate the need to have a multichannel sound recorder for time purposes In that fashion an ordinary two-channel phonocardiograph can be used with great accuracy Perhaps its greatest value lies in the identification of the diastolic events of the cardiac cycle and particularly in the differential diagnosis between the second sound the opening snap and the third sound which differentiation provides for the most common mistakes made in phonocardiography

In addition in cases of mitral stenosis with calcified valve and absent opening snap it is possible to measure the distance between the second sound and the beginning of the filling wave (2 FW) and this interval has exactly the same value as 2 OS interval (Fig 14) This fact should be strongly emphasized because of its practical usefulness

Aside from its value as a reference tracing the ACG can show interesting abnormalities of its components in the case of some valvular lesions or cardiac defects As we have demonstrated in a previous report [7] the analysis of the diastolic component of the ACG seems to be helpful in the differential diagnosis between mitral stenosis and regurgitation In mitral stenosis the rapid filling wave is absent (Fig 4) and in mitral regurgitation there is an accentuation of this component (Fig 5) In the presence of combined re

gurgitation and stenosis the ACG seems to be of special value In this circumstance the ACG continues to show absence of RFW when stenosis predominates and presence of RFW when regurgitation is the primary lesion Conditions associated with ventricular diastolic overloading as in aortic and pulmonic insufficiency septal defects etc tend to increase the rapid filling wave of the ACG On the other hand conditions associated with ventricular systolic overload as in aortic and pulmonic stenosis systemic and pulmonic hypertension etc tend to increase the amplitude of the a wave and changes in the shape of the systolic wave are observed as well as demonstrated in Figs 8 and 9 However the abnormalities of the systolic component of the ACG have been variable and a special study is being presently undertaken in order to clarify some of these problems

The technique of recording the ACG must be developed by practice and initial attempts usually result in artificial curves as demonstrated in Figs 15 and 16 Difficulty in recording the apexcardiogram is usually encountered in patients with pulmonary emphysema marked chest deformity and obesity We do not wish to convey an impression of overenthusiasm for the value of the method described or to imply that the recording of displacement curves or attempts to explain their possible values is a new concept Others [13] have tried to define a physiologic role for the components of the apexcardiogram but very few have attempted correlation with intracardiac pressure curves We believe that at the present time we have accumulated enough material to confirm that the components of the ACG represent the mechanical events of the left and right ventricles (Figs 17 and 18)

Summary and conclusion

The value of the apexcardiogram as a reference tracing in phonocardiography has been emphasized The greatest value of the apexcardiogram (ACG) seems to be in the identification of the diastolic events of the cardiac cycle since no reference tracing presently in use can provide this information

The abnormalities of the ACG in conditions associated with ventricular systolic or diastolic overloading were discussed The great usefulness of the ACG in cases of mitral valve disease was emphasized

We wish to thank Dr P Frank Trotta Dr F Crow Dr Yen Shen Mrs Carol Dafoe and Miss Rosemary Chapman for their technical assistance

REFERENCES

1 Leatham A and Vogelpoel L The early systolic sound in dilatation of the pulmonary artery Brit Heart J 16 21 1954
2 Leatham A Splitting of the first and second heart sound Lancet 2 607 1954
3 Dimond E G and Benchimol A Phonocardiography in pulmonary stenosis special correlation between hemodynamics and phonocardiographic findings Ann Int Med 52 145 1960
4 Benchimol A Dimond E G and Shen Y Ejection time in aortic stenosis and mitral stenosis Am J Cardiol 5 728 1960
5 Shen Y Crow E Dimond E G and Benchimol A The use of the indirect femoral tracings in the diagnosis of coarctation of the aorta Chinese M J (In press)
6 Hartman H The jugular venous tracing Am Heart J 59 698 1960
7 Benchimol A Dimond E G Waxman D and Shen Y Diastolic movements of the precordium in mitral stenosis and regurgitation Am Heart J 60 417 1960
8 Hartman H Differentiation between the influence of the right and the left ventricle in the phonocardiogram with the aid of pulsation curves Second European Congress of Cardiology 1956 Abstract of Papers p 12
9 Miller A and White P Crystal microphone for pulse wave recording Am Heart J 21 504 1941
10 McKusick V A Cardiovascular sound in health and disease Baltimore 1958 Williams & Wilkins Co
11 Eddleman E E Yoe R H Tucker W T Knowles J L and Willis K The dynamics of ventricular contraction and relaxation in patients with mitral stenosis as studied by the kinetocardiogram and ballistocardiogram Circulation 11 774 1955
12 Eddleman E E Christianson L Pierce J R and Walker R P The kinetocardiogram II The normal configuration and amplitude Circulation 8 370 1953
13 Harrison T R Palpation of the precordial impulses Stanford M Bull 13 385 1955
14 Wiggers C J Dynamics of ventricular contraction under abnormal conditions Circulation 5 321 1952
15 Johnston F D and Overy D C Vibrations of low frequency over the precordium Circulation 3 579 1951
16 Weitz W Quoted by Johnston and Overy [15]
17 Dressler W Pulsations of the wall of the chest Arch Int Med 60 224 1937
18 Luisada A The heart beat New York 1953 Paul B Hoeber Inc p 51

Cardiopulmonary changes in scleroderma
A physiologic study

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Scleroderma is a generalized connective tissue disorder of unknown etiology which frequently produces cardiopulmonary damage. The disease occurs mainly in women between the third and the sixth decades and evidence of visceral involvement usually follows the articular and cutaneous manifestations.[1] Occasionally, pulmonary or cardiac symptoms may herald the onset of the disease, but in such cases the diagnosis is usually missed.

The general clinical picture of scleroderma is well known, but the hemodynamic and pulmonary derangements it may produce have received insufficient emphasis. For this reason detailed cardiopulmonary studies were done in 4 patients with scleroderma heart disease in the hope of characterizing the derangements more precisely. Ventilatory and diffusion studies and right heart catheterization were performed in each instance. The clinical diagnosis in the 4 patients was based mainly on the involvement of the skin and various organs including the esophagus, and on skin biopsies. There was no evidence of valvular, hypertensive, or overt coronary arterial disease.

Case Material

Case 1. A 40-year-old Negro woman first noted Raynaud's phenomenon in early 1958. Progressively, the skin over the arms, chest, and legs became tight and shiny, with some limitation of motion of the joints. In July, 1958, she underwent a right thoracotomy after a gunshot wound. The postoperative course was complicated by a reaction to transfusion which was characterized by chills and fever and a residual pleural thickening. Blood serology was positive. Repeated lupus erythematosus cell preparation, latex fixation, and sheep cell agglutination tests were negative. Sedimentation rate was 65 mm. per hour. The electrocardiogram was normal. Fluoroscopy with barium swallow showed a dilated inert esophagus. Skin biopsy was negative.

In July, 1959, dysphagia, heartburn, exertional dyspnea, orthopnea, frequent bouts of paroxysmal nocturnal dyspnea, and dependent edema made their appearance. She denied cough, pleurisy, loss of weight, or hemoptysis. The skin had become waxy, thin, atrophic, and bound down over the dorsum of fingers, hands, and wrist. There were similar changes over the thorax and face causing restriction of temporomandibular motion. No lymphadenopathy or alopecia was noted. The tongue was normal. The lungs were clear except for dullness and decreased breath sounds at the right base. Blood pressure was 170/70 mm. Hg. The heart was not enlarged and no murmurs were heard. The second sound at the base in the pulmonic area was split. The liver was not enlarged, but the tip of the spleen was felt. The rest of the physical examination was noncontributory.

The hemoglobin was 13 Gm. per 100 ml. Urinalysis was normal. Blood urea nitrogen and serum electrolytes were normal. Albumin/globulin ratio was 3.6/4.8 Gm. Bromsulphalein test showed 16 per cent retention after 45 minutes. The other liver function tests were normal.

X-ray studies showed slight cardiomegaly and blunting of the right costophrenic angle (Fig. 1). The wrists and hands were normal. Barium swallow illustrated rigidity of the distal esophagus, creating a degree of functional obstruction. Barium remained

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in the esophagus t least 1 hour Ventilatory and cardiac catheterization tudies are presented in Tables I and II

Over a 4-week period she received 73 Gm of ersene (sodium EDTA) with dramatic improve ment in the skin and motion of the joints Three months later the results of stalometry and right heart catheterization are unchanged On follow ups progressiv changes in the skin ha been observed

Case 2 A 57 year-old wh te ma first noted tiffness and thickening of the skin over the hands and feet sufficient to restrict motion of the joints in August 1958 He experienced no pain or swelling of the joints When seen 2 months later he denied dy phagia and cardiorespiratory symptoms The kin over the extremities as thickened and bound dow limiting motion in the fingers wrists and feet There was definite weakness of the muscles of the hand biceps triceps and quadriceps bilaterally Examination of the heart and lungs was within normal limits

The hemoglobin level was 11 3 Gm total and d fferential leukocyte counts were normal Urinalysis as negativ Serology lupus erythematosus cell preparation latex fixation nd sheep cell agglutina tion ere negative Serum electrolytes were normal Albumin/globulin ratio was 4 0/2 8 Gm Ventilation tudies were normal X ray of the chest were normal The electrocardiogram revealed non pecific T wa change which disappeared t later date A barium swallow demonstrated only a small hiatus hernia Film of the hands were negativ Skin biopsy was compatible w th scleroderma

He was treated with relaxin (40 mg day) over a 3 eek period with prominent subjectiv but no objectiv improvement I February 1959 he was given 3 eek course of ersene during which time there was subjectiv improvement in the skin and moti of the joints however repeated measurement of the tal capacity showed no change

He readmitted in January 1960 with progres iv tightening of the skin H again denied card orespiratory mptoms and phy ical examina tion of the heart and lungs was normal He was again given 45 Gm of ersene without definit objectiv cha ges Prior to this box therapy right heart catheterization and entilation studies ere performed (Tables I and II)

Case 3 A 52 year-old Negro woman had noted progre siv tightening of the skin over the dorsum of the fingers and hands for 10 years and inability to make fist or to open her mouth widely for 2 years She experienced pain and discoloration of the finger tips on exposure to cold She also complained of frequent heartburn sensation of food stopping in the chest and progressive exertional dyspnea for 4 months She sometimes experienced nocturnal coughing paroxysms allegedly productiv of froth putum hich contained streaks of blood She specif ically denied orthopnea peripheral edema fever pleuritic pain and loss of weight

Physical examination revealed chronically ill oma with normal ital signs She was ble to lie flat without di tre There was generalized lymphadenopathy There was depigmentation over the malar areas and tautness of the skin over the face The tongue appeared to be normal The lun were clear The heart was diffusely enlarged and there was pulsation in the left parasternal region Normal sinus rhythm wa pre-ent and soft systolic murmur was heard over the precordium The second heart sound in the pulmonic area was pl t, and its second component was accentuated Examination of the abdomen was negativ The kin er the forearms and fingers was taut fixed and shin There ere punctate scars on several of



Fig 1 Case 1 Posteroanterior and left anterior oblique iew of the che t A bullet i seen in the left lower lun field just lateral to the thoracic ertebra.

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Case Material

Case 1. A 40-year-old Negro woman first noted Raynaud's phenomenon in early 1958. Progressively, the skin over the arms, chest, and legs became tight and shiny, with some limitation of motion of the joints. In July 1958, she underwent a right thoracotomy after a gunshot wound. The postoperative course was complicated by a reaction to a transfusion which was characterized by chills and fever, and residual pleural thickening. Blood serology was positive. Repeated lupus erythematosus cell preparations, latex fixation, and sheep cell agglutination tests were negative. Sedimentation rate was 65 mm. per hour. The electrocardiogram was normal. Fluoroscopy with barium swallow showed dilated, inert esophagus. Skin biopsy was negative.

In July 1959, dysphagia, heartburn, exertional dyspnea, orthopnea, frequent bouts of paroxysmal nocturnal dyspnea, and dependent edema made their appearance. She denied cough, pleurisy, loss of weight, or hemoptysis. The skin had become waxy, shiny, atrophic, and bound down over the dorsum of fingers, hands, and wrists. There were similar changes over the thorax and face, causing restriction of temporomandibular motion. No lymphadenopathy or alopecia was noted. The tongue was normal. The lungs were clear except for dullness and decreased breath sounds at the right base. Blood pressure was 170/[illegible]0 mm. Hg. The heart was not enlarged, and no murmurs were heard. The second sound at the base in the pulmonic area was split. The liver was not enlarged, but the tip of the spleen was felt. The rest of the physical examination was noncontributory.

The hemoglobin was 13 Gm. per 100 ml. Urinalysis was normal. Blood urea nitrogen and serum electrolytes were normal. Albumin/globulin ratio was 3.6/4.8 Gm. Bromsulphalein test showed 16 per cent retention after 45 minutes. The other liver function tests were normal.

X-ray studies showed slight cardiomegaly and blunting of the right costophrenic angle (Fig. 1). The wrists and hands were normal. Barium swallow illustrated rigidity of the distal esophagus creating a degree of functional obstruction. Barium remained

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in the esophagus at least 1 hour Ventilatory and cardiac catheterization studies are presented in Tables I and II

Over 4 week period he received 73 Gm of ersene (sodium EDTA) with dramatic improvement the skin and motion of the joints Three months later the results of italometry and right heart catheterization were unchanged On follow ups progressive changes in the kin has been observed

Case 2 A 5 year-old white man first noted stiffness and thickening of the skin over the hands and feet sufficient to restrict motion of the joints in August 1958 He experienced no pain or swelling of the joint When seen 2 month later he denied dysphagia and cardiorespiratory symptoms The skin over the extremities was thickened and bound down limiting motion in the fingers wrists and feet There was definite weakness of the muscles of the hand biceps triceps and quadriceps bilaterally Examination of the heart and lungs within normal limit

The hemoglobin level was 11 3 Gm total and differential leukocyte counts were normal Urinaly is was negativ Serology lupus erythematou cell preparation latex fixation and heep cell agglutination ere negativ Serum electrolytes were normal Albumin/globulin ratio was 4 0/2 8 Gm Ventilation studies were normal X rays of the chest were normal The electrocardiogram revealed nonspecific T changes which disappeared t later date. A barium swallow demonstrated only a small hiatus hernia Films of the hand ere negativ Skin biopsy was compatible with scleroderma

He was treated with relaxin (40 mg da) over week period w th prominent subjectiv but no objectiv improvement In February 19 9 he was given 3-week course of ersene during which time there was subjectiv improvement in the skin and motion f the j nts however repeated measurement of the ital capacity howed no change

He was readmitted in January 1960 with progressive tightening of the skin H again denied cardiorespiratory symptoms and ph ical examination of the heart and lungs was normal H as again given 45 Gm of ersene thout defi nit objectiv changes Prior to the abov therapy right heart catheterization and entilation tudies are performed (Tables I and II)

Case 3 A 5 year-old Negro oma had noted progressive tightening of the skin over the dorsum of the fingers and hand for 10 years d inability to make fist or to open her mouth widel for 2 ears She experienced pain and discoloration of he finger tips on exposure t cold She also complained of frequent heartburn sensation of food stopping in the chest and progres ertional dyspnea for 4 months She sometimes experienced nocturnal coughing paroxysms allegedly productiv of froth sputum hich contained streaks of blood She specifically denied orthopnea peripheral edema f er pleuritic pain and lo of weight

Physical examination revealed a chronicall ill oman w th normal ital ns She was ble to be flat w thout distress There as general zed lymphadenopathy There was depigmentation over the malar areas and tautness of the skin over the face The tongue ppeared to be normal The lungs were clear The heart was diffused enlarged and there was pulsation in the left parasternal region Normal inus rhythm wa present and soft ystolic murmur was heard over the p ecordium The second heart sound in the pulmonic area was plit and its second component was accentuated Examination of the abdomen w negativ The kin over the forearm and fingers w ta t fixed and shiny There were punctate scars on several of



Fig 1 Case 1 Posteroanterior and left anterior oblique iew of the chest A bullet seen in the left lower lung field just lateral to the thoracic ertebra

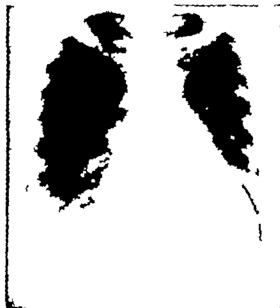




Fig 2 Case 3 Posteroanterior and right anterior oblique views of the chest

the finger tips There was no cyanosis clubbing of the fingers or edema

Hemogram and urinalysis were normal Blood serology was positive Lupus erythematosus cell preparation sheep cell agglutination and latex fixation tests were negative Blood urea nitrogen and serum electrolytes were normal Albumin/globulin ratio was 3 8/3 5 Gm and Bromsulphalein test showed 13 per cent retention after 45 minutes Thymol turbidity was 9 units

The electrocardiogram showed right axis deviation and right ventricular preponderance Skin biopsy was reported as compatible with scleroderma Cardiac fluoroscopy disclosed diffuse cardiomegaly The pulmonary artery segment was prominent (Fig 2) The esophagus was dilated and atonic Ventilatory studies demonstrated marked restrictive-obstructive defect (Table I) and right heart catheterization showed moderate pulmonary hypertension and decreased cardiac output (Table II)

Case 4 A 43 year-old Negro woman was first seen in 1957 complaining of pain and stiffness of the fingers wrists and ankles profound weakness dysphagia fever and 50-pound loss of weight during the preceding year She was totally immobilized by the complaint The skin of the extremities and face was tight and atrophic A skin muscle biopsy showed changes that were compatible with scleroderma The patient also had microcytic hypochromic anemia but total and differential leukocyte counts were normal Lupus erythematosus cell preparation was negative Sheep cell agglutination and serology were positive Albumin/globulin ratio was 2 7/3 8 Gm X-ray studies of the lungs and heart were normal but the upper two thirds of the barium-filled esophagus was dilated and atonic

Her general condition improved on steroid therapy (Meticorten 10 to 70 mg per day) and after several weeks she was able to walk without assistance Subsequent examinations revealed gradual increase of intensity of the second heart sound in the pulmonic area A chest film taken in May 1959 showed diffuse cardiomegaly for the first time but she had no symptoms referable to the heart In June 1959 she experienced a single episode of hemoptysis unassociated with chest pain or cough and the lung fields were clear radiographically The electrocardiogram showed right axis deviation right ventricular preponderance and tall peaked P waves (P pulmonale) The heart remained enlarged clinically and the accentuated and split pulmonic second sound was noted to be fixed throughout the respiratory cycle Data obtained by right heart catheterization are presented in Table II Ventilatory studies demonstrating restrictive defect of severe degree are given in Table I

Discussion

The frequency of cardiac involvement in patients with scleroderma is unknown but at postmortem evidence of myocardial involvement was found by Piper and Helwig[4] in 28 of 31 cases Cardiac manifestations are attributable either to direct involvement of left ventricular muscle or to pulmonary fibrosis In patients with fibrotic myocardial changes left ventricular failure may occur in those with pulmonary fibrosis right ventricular failure is the end result A diffusely enlarged and a weakly pulsating left ventricle is a late manifestation of the disease and simulates in some respects pericardial effusion

Eighteen months after the appearance

Table I Spirometric studies in patients with scleroderma

	Case 1	1 b	2	3	4	Normal
Forced vital capacity (FVC)	2 2	2 2	3 63	1 6	1	
FVC / Predicted FVC × 100	53	55	83	50	44	100 ± 11
FEV	1 5	1 4	2 6	0 7	1 2	
% FEV / FVC	68	64	72	44	71	67 8 ± 5 8

FEV Forced expiratory [illegible] 1 [illegible] second

Table II Hemodynamic findings in patients with scleroderma

Case	Pulmonary arterial pressure (mm Hg) S/D	Pulmonary arterial pressure (mm Hg) Mean	Right auricle mean pressure (mm Hg)	Pulmonary wedge mean pressure (mm Hg)	Brachial artery Content (vol %)	Brachial artery Saturation (%)
1	28/10	(17)	3	6	15 44	94
1 b	26/12	(19)	3	7	13 16	92
2	14/4	(9)	0	2	17 54	91
3	64/30	(40)	3	5	17 92	94
4	71/31	(51)	4	–	13 05	89

Case	Cardiac output (L/min)	Cardiac index (L/min/M²)	Breathing 100% oxygen: Arterial pCO_2 (mm Hg)	Arterial pO_2 (mm Hg)	A-a PO_2 gradient (mm Hg)	Shunt (%)
1 a	3 57	1 96	35	273	379	20
1 b	6 10	3 45	40	365	297	17 7
2	2 53	1 59	32	233	431	19 4
3	1 57	0 90	—	194	455	18 7
4	2 41	1 53	46	370	287	11 7

*Assumed to be 40 mm. Hg
§ [illegible]

of changes in the skin the patient of Case 1 gradually developed cardiomegaly and congestive failure Her cardiac output was quite low As was anticipated treatment with versene resulted in marked clinical improvement[7] somewhat unexpectedly her cardiac output became normal (Table II) It is not clear whether the improvement in cardiac output was the result of versene therapy alone or of the combined effect of versene and digitalis therapy In actual fact it seems doubtful that either drug would greatly improve the cardiac status if diffuse fibrosis were present in the left ventricular muscle Also in Case 2 there was a reduced resting cardiac output but there was no clinical evidence of cardiac disease suggesting perhaps that myocardial

involvement may occur before clinical symptoms appear. The electrocardiogram in this patient showed abnormal T waves in the course of his illness, changes usually thought to be consistent with diffuse myocardial damage.

In Cases 3 and 4, electrocardiographic evidences of right ventricular overload were present and marked pulmonary hypertension was found by cardiac catheterization (Table II). In these cases it is believed that the disease process was primarily concentrated in the lungs. Such involvement has been reported in up to 50 per cent of patients with the disease. However, a higher incidence would undoubtedly be found if pulmonary function tests were routinely performed in such patients. Alterations in pulmonary function are dependent upon the location and the extent of the fibrotic process. Involvement of the skin, the muscles of the thorax, the pulmonary parenchyma, and the pleura interferes with respiratory excursion and produces a restrictive type of ventilatory defect. In this instance the total vital capacity is reduced. This was observed in all of our cases but to a lesser extent in Case 2. In instances in which the fibrotic process involves the bronchial musculature leading to emphysema and bronchiectasis, an obstructive type of defect may become apparent. Evidence of such a defect was obtained in Case 3 (Table I). A combined type of defect (restrictive and obstructive) may be present, therefore, in certain patients with this disease. Versene therapy in Case 1 resulted in no objective improvement in pulmonary ventilation, although clinically the subject felt better. In both instances (Cases 1 and 4) in which diffusion studies by the single breath carbon monoxide technique were performed, a marked reduction in diffusion was observed. The diffusion capacities were 11 and 17 ml. CO/min./mm. Hg, respectively, as compared to a normal value of 30 ml. CO/min./mm. Hg. In Case 4 the low diffusion capacity could partly be explained by the low hemoglobin (6.5 Gm. per 100 ml.) present at the time of this study.

Breathing 100 per cent oxygen for 30 minutes resulted in a large alveolar-arterial (A-a) oxygen tension gradient in all of our cases (Table II). This gradient ranged between 287 and 455 mm. Hg, indicative of venoarterial shunting through the lungs. The magnitude of the shunts varied between 11.7 and 20.2 per cent of the respective cardiac output. In Case 1 the shunt did not significantly decrease after versene therapy which was accompanied by clinical improvement.

The large alveolar-arterial (A-a) oxygen tension gradient observed in patients with scleroderma has been thought to represent an alveolar-capillary block, a diffusion defect caused by thickening of the alveolar septa. But in at least 2 of our patients (Cases 1 and 4) the A-a gradient resulted from a composite of two physiologic defects: a diffusion defect, as demonstrated by the reduction in diffusion capacity of carbon monoxide, and an intrapulmonary venoarterial shunting, both of which may have arisen from the same anatomic lesion resulting in perfused nonventilated units of lung tissue.

It is apparent, therefore, that in our cases of scleroderma the disease process involved both the heart and the lungs, with one organ predominating in its clinical manifestations. In instances in which the heart is primarily affected, the fibrotic process in the ventricular muscles results in a reduction in the cardiac output (Cases 1 and 2) prior to the clinical manifestations of left heart failure. But when the lungs are predominantly involved, pulmonary hypertension and the clinical picture of cor pulmonale appear. However, the findings in our patients suggest that in scleroderma an intrapulmonary venoarterial shunting and a diffusion defect are usually present even in instances in which the heart appears to be the organ mostly involved.

Summary

Four patients with scleroderma were studied by means of cardiac catheterization and measurements of pulmonary function.

*Th[illegible] d[illegible]gree of pulmonary venoarterial shunting [illegible] calculated f[illegible] equation [illegible]

$$\% \text{ shunt} = 100\left(1 - \frac{\Delta \text{A-a } O_2 \text{ difference}}{\Delta \text{A-a } O_2 \text{ difference} + Q}\right)$$

[illegible] Q [illegible] the [illegible] alveolar-arterial [illegible] oxygen tension gradient [illegible] by the [illegible] The [illegible] equal [illegible] 0.003. The [illegible] oxygen [illegible] (PAO_2) was calculated [illegible] alveolar air equation. The arterial [illegible] tension (PaO_2) was determined polarographically.

In one case the studies were repeated after versene therapy and subjective clinical improvement. In 2 cases a single breath carbon monoxide test was performed.

In 2 cases marked pulmonary hypertension was found and in all 4 cases reduction in the cardiac output and index was demonstrated.

All patients exhibited evidence of restrictive ventilatory disturbance but only one showed evidence of an obstructive type of pulmonary ventilatory defect. All patients exhibited a large intrapulmonary venoarterial shunt. In the 2 patients in whom the single breath carbon monoxide technique was performed a diffusion defect was also observed. The large A-a PO_2 gradient described in these patients when they were breathing room air was the result of the combination of a diffusion defect and pulmonary venoarterial shunts.

Versene therapy resulted in marked subjective improvement but failed to improve the pulmonary ventilation or to diminish the intrapulmonary shunt.

REFERENCES

1. Weiss, S., Stead, E. W., Warren, J., and Bailey, O.: Scleroderma heart disease, Arch. Int. Med. 71: 749, 1943.
2. Orabona, M., and Albano, O.: Systemic progressive sclerosis, Acta med. scandinav. (Suppl.) 160: 333, 1958.
3. Piper, W., and Helwig, E.: Progressive systemic sclerosis, A. M. A. Arch. Dermat. & Syph. 72: 535, 1955.
4. Goetz, R.: The heart in generalized scleroderma, Angiology 2: 555, 1951.
5. Mathisen, A., and Palmer, J.: Diffuse scleroderma with involvement of the heart, Am. Heart J. 33: 366, 1947.
6. Bergleman, P., Goldner, F., and Bayles, T.: Progressive systemic sclerosis, New England J. Med. 249: 45, 1953.
7. Klein, R., and Harris, S.: Treatment of scleroderma, sclerodactylia and calcinosis by chelation (EDTA), Am. J. Med. 19: 798, 1955.
8. Leinwand, I., Duryee, A., and Richter, M.: Scleroderma (based on a study of over 150 cases), Ann. Int. Med. 41: 1003, 1954.
9. Shuford, W., Seaman, W., and Goldman, A.: Pulmonary manifestation of scleroderma, A. M. A. Arch. Int. Med. 92: 85, 1953.
10. Hayman, L., and Hunt, R.: Pulmonary fibrosis in generalized scleroderma. Report of a case and review of the literature, Dis. Chest 21: 691, 1952.
11. Dostrovsky, A.: Progressive scleroderma of the skin and cystic sclerodermal changes of the lungs, Arch. Dermat. & Syph. 55: 1, 1947.
12. Bashour, F.: Clubbing of the digits. Physiological considerations. (To be published.)
13. Comroe, J., Forster, R., DuBois, A., Briscoe, W., and Carlsen, E.: The lung, Chicago, 1955, Year Book Publishers, Inc.
14. Harvey, R., Ferrer, I., Richards, D., and Cournand, A.: Influence of chronic pulmonary disease on the heart and circulation, Am. J. Med. 10: 719, 1951.

Experimental and laboratory reports

The effects of infusing quinidine sulfate and potassium chloride, separately and combined, on conduction times of the dog heart

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The production of conduction defects by high levels of quinidine, both within the atrium[1] and within the ventricle,[2] is well recognized. Likewise, it is well recognized that disappearance of P waves as well as slowing of conduction, both atrioventricular and intraventricular, occur in the presence of hyperkalemia.[3,4] The question arises whether the simultaneous presence of high levels of quinidine and hyperkalemia would be additive or synergistic with respect to the production of conduction defects. In an effort to answer this question we have carried out experiments in which potassium chloride and quinidine sulfate, separately and in combination, were infused into normal dogs. Plasma levels of both potassium and quinidine were determined, and electrocardiographic tracings were obtained for analysis of conduction times.

Method

Nineteen mongrel dogs which weighed from 5.2 to 17.5 kilograms were used. All experiments were carried out under sodium pentobarbital anesthesia, and blood pressure was monitored continuously in all animals by use of a damped mercury manometer. Serial electrocardiographic tracings were taken on each animal by means of a Sanborn Viso-cardiette and standard limb leads. Potassium chloride as an isotonic solution was infused intravenously at rates which varied from 1 to 4 c.c. per minute; the rates were determined by the size of the dogs and by their responses. Quinidine sulfate was dissolved in mammalian Ringer-Locke's solution and likewise was given by intravenous infusion. When both potassium chloride and quinidine sulfate were administered, the quinidine sulfate was dissolved in the potassium chloride solution. Blood for analysis was withdrawn from the femoral vein. Serum potassium was determined by use of a Perkin-Elmer Model 52A flame photometer with lithium used as an internal standard. Quinidine was determined by means of the fluorometric method of Brodie,[5] after deproteinization by metaphosphoric acid.

In some experiments potassium chloride alone was infused (8 cases). In others quinidine sulfate alone was infused (5 cases). High levels of quinidine and potassium together were achieved in three different ways: (a) by infusing both substances together from the beginning of the experiment (3 cases); (b) by first elevating the plasma potassium and then superimposing

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infusions of quinidine (3 cases) (c) by first elevating the plasma quinidine and then superimposing infusions of potassium chloride (3 cases) Since no differences in results from these three procedures were apparent they are considered together in the presentation of data

Results

Effects upon cardiac rate and rhythm When potassium chloride alone was given no consistent changes in cardiac rate were produced until P waves disappeared partial A V block was produced and/or ectopic beats occurred No changes in blood pressure were observed until some change in cardiac rhythm took place As the plasma quinidine was progressively elevated the cardiac rate progressively slowed and the blood pressure progressively fell In all but one animal by the time the level of quinidine in the blood reached 9 or 10 mg per liter the heart rate was between 50 and 70 This should be compared with the initial sinus tachycardia of 140 to 160 beats per minute which was found in these animals as it is found in most dogs under sodium pentobarbital anesthesia When quinidine alone was given no rhythm other than a normal sinus rhythm was ever seen When potassium and quinidine were both given no additive effect of the hyperkalemia upon the quinidine induced slowing of a sinus rhythm was observed

Effects upon the P waves In conformity with findings previously reported [4] P waves disappeared in dogs into which potassium chloride alone was infused when the plasma potassium was sufficiently elevated The levels of plasma potassium at which the P waves disappeared in these animals varied from 6 2 to 8 7 mEq per liter (Fig 1) When levels of potassium of 7 mEq per liter and above were achieved and the P waves persisted some widening of the P waves occurred When quinidine alone was infused slight but definite and progressive widening of the P waves was observed The quantitative data bearing upon the point are presented in Fig 2 and show that the P wave duration is approximately doubled with levels of plasma quinidine of 10 mg per liter When both potassium and quinidine were infused in 8 instances it was possible to determine P wave

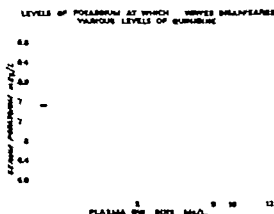


Fig 1 The levels of serum potassium at which P waves disappeared when no quinidine was infused are indicated by those points appearing vertically over zero concentration on the axis The other points show the concentration of *both* potassium and quinidine when P waves disappeared

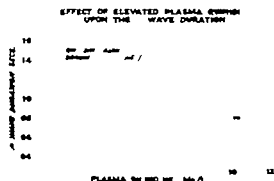


Fig 2 No data from animals with serum potassium above 7 5 mEq per liter are shown because P waves did not persist at levels of serum potassium higher than this when quinidine was given. No data for animals with serum potassium below 6 mEq per liter are given because such levels could scarcely be called hyperkalemic

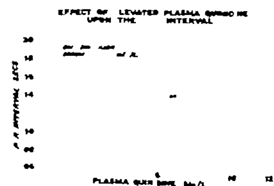


Fig 3 The comments made relative to Fig 2 also apply here

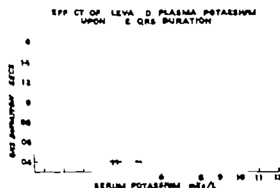


Fig. 4. The QRS duration was read to the nearest 0.01 second. This accounts for the grouping of QRS times as seen in Figs. 4 and 5.

duration in animals with levels of plasma potassium above 6 mEq per liter. These data are shown in Fig. 2 and demonstrate that hyperkalemia of this degree does not alter quinidine slowing of atrial conduction. The combination of high levels of quinidine in the blood and hyperkalemia did not alter the effective concentration of plasma potassium which produced disappearance of P waves. The data which establish this point are shown in Fig. 1. Although it may appear that when the plasma quinidine is elevated the mean level of potassium necessary to produce disappearance of P waves is lowered, analysis of the data by the nonparametric Mann-Whitney U test shows that the trend is not significant even at the 05 level.

Effects upon A-V conduction time. With infusion of potassium chloride alone, both disappearance of P waves and 2:1 and higher degrees of A-V block were produced. With infusion of quinidine alone, there was progressive prolongation of the A-V conduction time (measured by the P-R interval) as the level of plasma quinidine was elevated; the P-R interval was approximately twice that of the controls with levels of plasma quinidine above 8 mg. per liter. These data are presented in Fig. 3. There were 6 experiments in which levels of plasma potassium of 6.0 to 7.5 mEq. per liter were produced with simultaneous infusion of quinidine, and in which P waves persisted without 2:1 or higher degrees of A-V block; in all of these, prolongation of the P-R interval was not greater than that seen with quinidine alone. These data are likewise shown in Fig. 3. Thus, these experiments indicate that the effect of hyperkalemia and quinidine upon the A-V conduction time are neither antagonistic, synergistic, nor additive.

Effects upon intraventricular conduction time. Hyperkalemia alone produces definite impairment of intraventricular conduction, but doubling of the normal QRS time of approximately 0.04 second was not observed in these experiments until the level of plasma potassium exceeded 6.5 mEq. per liter. With a higher concentration of plasma potassium the QRS time may exceed 0.16 second. All of these data are presented in Fig. 4. When quinidine alone was infused, prolongation of the QRS time was also produced, but not to the same degree seen with hyperkalemia. The highest levels of quinidine achieved did not produce a QRS duration greater than 0.10 second. The complete data on quinidine are presented in Fig. 5. The data from the experiments in which both potassium and quinidine were infused are also presented in Fig. 5.

The intraventricular conduction times of those dogs in which the plasma potassium exceeded 6.5 mEq. per liter are shown by open circles. Reference to Fig. 4 will show that the intraventricular conduction times of these dogs (i.e., those receiving quinidine and having levels of potassium above 6.5 mEq. per liter) do not differ essentially from the intraventricular conduction times of dogs in which hyperkalemia of comparable degree was produced without simultaneous infusion of quinidine. Thus, quinidine does not alter potassium-induced prolongation of intraventricular

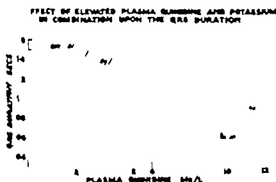


Fig. 5. The QRS duration of those animals with potassium over 6.5 mEq. per liter should be compared with the QRS duration of animals infused with potassium only as shown in Fig. 4.

conduction time. The intraventricular conduction times of those dogs in which the plasma potassium was 6.5 mEq. per liter or below are shown by open triangles. It is apparent from the data in the graph that the intraventricular conduction time in these animals is little, if any, more prolonged than that in those to which quinidine alone was given. Thus when the lower degrees of hyperkalemia are considered, potassium and quinidine are neither antagonistic, synergistic, nor additive in their ability to produce impairment of intraventricular conduction.

Discussion

The initial question can now be answered. The effects of hyperkalemia and of high levels of quinidine upon intra-atrial, atrioventricular, and intraventricular conduction are neither additive nor synergistic. Thus in patients with hyperkalemia one would not expect exaggeration of the toxic effects of quinidine as manifested by cardiac conduction defects. On the basis of these studies, hyperkalemia per se is no contraindication to quinidine therapy.

These experiments do not throw any light upon the basic mechanism whereby either potassium or quinidine affect transmission of the excitatory process within the heart. Neither can one make a reasonable inference concerning whether one or more than one mechanism is involved. This follows from the fact that regardless of whether they affected the same or different mechanisms, one would hypothecate that their effects would at least be additive.

Summary

Normal dogs were infused with potassium chloride solution and with quinidine sulfate solution separately and in combination. Concentrations of serum potassium and of plasma quinidine were determined. Effects upon P waves, together with intra-atrial, atrioventricular, and intraventricular conduction times were determined. Both quinidine and hyperkalemia produce prolongation of all three parameters of conduction velocity within the heart. These effects are neither additive nor synergistic.

REFERENCES

1. Brom, B. B.: A study of factors related to effects of quinidine in experimental auricular flutter, Circulation 8:965, 195.
2. Gold, H., and Modell, W.: The action of quinidine on the heart in the normal unanesthetized dog, J. Pharm. & Exper. Therap. 46:357, 193.
3. Winkler, A. W., Hoff, H. F., and Smith, P. K.: EKG changes and concentration of potassium in serum following intravenous injections of potassium chloride, Am. J. Physiol. 124:478, 1938.
4. Chamberlain, F. L., Scudder, J., and Zwemer, R. L.: EKG changes associated with experimental alterations in blood potassium in cats, Am. Heart J. 18:458, 1939.
5. Brodie, B. B., and Udenfriend, S.: Estimation of quinine in human plasma with note on estimation of quinidine, J. Pharmacol. & Exper. Therap. 78:154, 1943.

The effect of intracavitary carbon dioxide on surface potentials in the intact canine chest

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It has been suggested that the mass of blood in the cavities of the heart distorts the electrical field in the chest and introduces error into the voltages recorded in electrocardiographic leads.[1,2] Theoretically, a nearby dipole with its axis directed radially from the blood-filled cardiac cavity will produce a greater voltage in surface leads than if the mass of blood were replaced by a medium of lesser electrical conductivity. This prediction may be extended to waves of activation moving away from the cavities; the presence of the blood is expected to enhance the peripheral effect, thus amplifying the resultant deflections in appropriate electrocardiographic leads.

In contrast to the heightened voltage from a *radial* dipole near a region of greater conductivity, the peripherally detected difference in potential from a dipole with its axis *tangential* to the boundary of the better conducting region should be reduced. Such theoretical expectations have been demonstrated easily in two dimensions with conducting paper, as noted in the Appendix of this report. With such two-dimensional models, the effect of a region of increased conductivity on a nearby dipole was compared with the distribution of potential in a homogeneous medium, and—when a hole was cut in the conducting paper—the theoretical prediction for completely removing the region of greater conductivity was seen. The effect on nearby dipoles under such circumstances was now reversed: the peripheral voltage from the radial dipole was diminished, and from the tangential dipole magnified.

The present study concerns the extension of these predictions to three dimensions and the living animal by replacing the good conductor (blood) in the ventricular cavities by a poor conductor (carbon dioxide gas). Separation between the contributions of radially directed excitation in the muscle surrounding each ventricular cavity was in this manner sought and in large part found. The removal of the shunting effect

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of blood made possible the additional distinction between probable radial spread of excitation during normal depolarization and probable tangential spread of excitation during right bundle branch block.

Methods and materials

Fifteen mongrel dogs which weighed between 9.0 and 19.5 kilograms were anesthetized with intravenous sodium pentobarbital (30 mg. per kilogram of body weight) and placed supine on the fluoroscopy table. Electrocardiograms were recorded with standard and augmented unipolar limb leads and unipolar chest lead. Spatial vectorcardiograms were recorded by both the equilateral tetrahedral reference system (Wilson-Burch) and the lead field system (McFee-Johnston*). Recordings were made with a DuMont 321-A oscilloscopic camera mounted on a dual beam slave oscilloscope driven from two Hewlett-Packard 130B oscilloscopes. Signals from surface electrodes were amplified by Tektronix 122 preamplifiers. The front and back electrode grids for the McFee-Johnston system were each made of five 1-cm. brass discs mounted to form a 2 inch square (between the centers of the four outer discs) on polyethylene sheeting and connected by 20,000-ohm resistances. The lateral lead pairs were composed of foreleg and axillary electrodes joined by 8,000 ohm resistances; head and foot electrodes were without added resistances, and the Wilson central terminal electrodes were connected by 12,000-ohm resistances.

Cardiac catheters were introduced by jugular or femoral vein and carotid or femoral artery into the right and left ventricles respectively. Before each insufflation the animal was placed in the 45-degree Trendelenburg position. A quantity of 30 to 50 c.c. of gaseous carbon dioxide, as required to fill each ventricle by fluoroscopic estimate, was introduced first into the right ventricle, then into the left ventricle, and then into both ventricles simultaneously. Selected electrocardiographic and vectorcardiographic tracings (usually including the horizontal plane projection or its components as the most sensitive parameter of change in distribution of thoracic potential) were recorded serially or continuously. In order to consider an experiment satisfactory, we required a return of the depolarization complex to the previous normal pattern before bilateral insufflation of carbon dioxide was attempted.

In 5 dogs right bundle branch block was induced by the injection of formaldehyde by percutaneous needle into the right septal myocardium under fluoroscopic and electrocardiographic guidance. When the tip of the needle (introduced through the second left intercostal space parasternally) was demonstrated to touch the catheter, the right septal wall was pricked or scratched until a right bundle branch block appeared on the monitoring oscilloscope; then 0.5 to 1 c.c. of 40 per cent formaldehyde was injected at the site. The lesion was verified at autopsy by iodine staining of the bundle.[7] The observations with infusion of carbon dioxide were then repeated in the presence of the right bundle branch block. Left-sided or bilateral instillations of gas were omitted on two occasions prior to the induction of the right bundle branch block so as to minimize the hazards to which the animal was subjected.

Results

The normal ventricular depolarization potentials during right ventricular filling with carbon dioxide. The effect on surface potentials of filling the right ventricular cavity with carbon dioxide, as visualized by electrocardiogram and spatial vectorcardiogram, may be seen in Figs. 1 and 2, which are representative of the findings in this study. The transformation in the depolarization complex can be followed most clearly in the horizontal plane projection of the spatial vectorcardiogram but can be seen readily in the sagittal lead of the other graphic form. The peak of the ventricular filling, as seen through the fluoroscope, coincided with the maximum degree of shrinkage of the R wave of the QRS complex. In the spatial vector loop the very earliest and the very latest portions of depolarization were unchanged, and the maximum apparent change occurred between early and middle and between mid-

*Since the sources of th[illegible] were expected [illegible] be roughly [illegible] eighth of those [illegible] the [illegible] of the grids were [illegible] 3 $\sqrt{1/8}$ [illegible] 1/2 [illegible] those recommended for man.

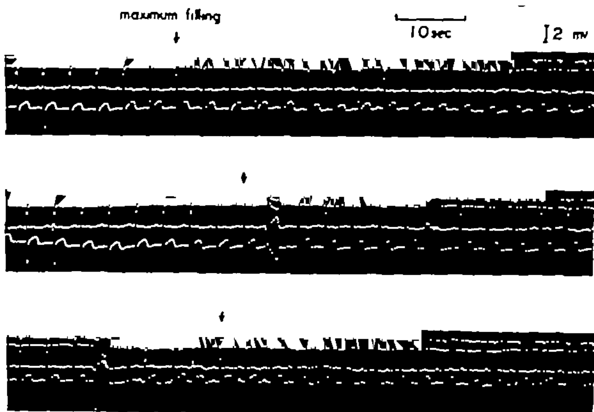


Fig 1 Simultaneous electrocardiograms of Dog N 15 made during right ventricular (*top*) left ventricular (*middle*) and biventricular (*bottom*) insufflation with CO The lead from above downward each group are unipolar back inverted bipolar left right bipolar foot head and bipolar front back (For convenience the sign is arranged so that the leads may be read as analogous to clinical Leads V inverted I and V) Note that the anterior precordial R diminished with either right or left ventricular insufflation of CO_2 and disappeared completely when both ventricles were filled with gas

dle and late depolarization However specific loss of forward components actually characterized the whole intermediate period as determined by superimposing electrocardiograms and vectorcardiograms

The shrinkage of peripherally recorded voltages began to subside almost immediately and the previous normal patterns *routinely reappeared within 5 to 10 seconds* as the carbon dioxide was expelled into the pulmonary artery Frequently one or more premature ventricular systoles occurred just after maximum filling

The normal ventricular depolarization potentials during left ventricular filling with carbon dioxide The immediate peak electrocardiographic effects were more transient with injection of carbon dioxide into the left ventricular cavity and a greater amount of carbon dioxide was required to maintain even a transient radiolucency of the entire ventricular cavity than on the right (usually 50 c c as compared with 30 c c) Since the cavities approximated each other in volume when cast postmortem this discrepancy was attributed to relatively more powerful and efficient emptying by the left ventricle An altered configuration of the spatial vector loop consistently *different from that of right sided* insufflation was observed at the height of left ventricular filling with carbon dioxide voltages during middle depolarization were drastically curtailed and a distinctive gouge indented the horizontal plane projection *of the QRS spatial vector loop more* from the left than from the front (Fig 2)

Emptying of carbon dioxide from the left ventricular cavity was frequently followed within 15 to 30 seconds by the development of ischemic T waves and spatial vector *loops* S T *shifts* and then

QRS alterations usually characterized by removal of posteriorly directed contributions during the later one half of depolarization (Fig 3) If the animal had been quickly brought out of the Trendelenburg position after peak filling with carbon dioxide these changes faded over a period of 10 to 15 minutes without residual However repeated infusion of the left side was usually poorly tolerated and resulted in either ventricular fibrillation or longer lasting deformities of the QRS and elevations of the S T segment which required several hours to fade After a series of left ventricular insufflations one animal died during the night

The normal ventricular depolarization potentials during combined left and right ventricular filling with carbon dioxide Because of the unfavorable sequelae frequently experienced after insufflation of the left ventricle alone only on 5 occasions were successful simultaneously bilateral injections of carbon dioxide accomplished In Fig 2 two series of horizontal plane projections of the spatial vectorcardiogram are seen illustrating the respective reductions in the QRS spatial loop with first right then left then bilateral ventricular filling with carbon dioxide It should be noted that neither right nor left insufflation appeared to alter greatly the very early frontward component of depolarization but insufflation of both chambers removed most of it Although the QRS complexes and loops were reduced markedly as though in an additive manner they did not disappear entirely

Bilateral infusion was usually followed by the more or less transient ischemia

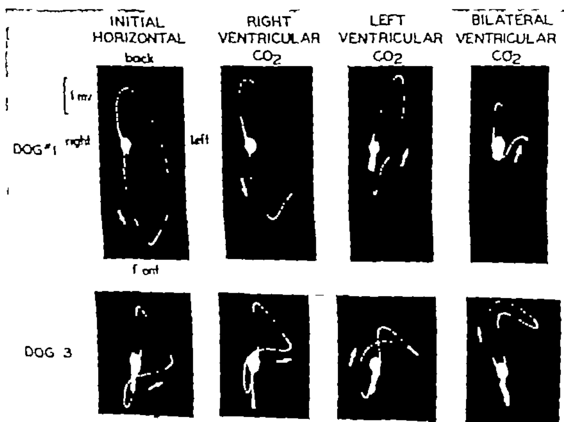


Fig 2 Serial projections of the horizontal plane of the vectorcardiogram (lead field system) during successive insufflation with right ventricular left ventricular and biventricular CO_2 in Dogs No 1 and 3 Note the removal of early frontward portions of the depolarization complex during each instance of right ventricular insufflation and backward displacement of the late QRS spatial vector loop With left ventricular insufflation of CO_2 more of middle depolarization removed (especially laterally) and with combined insufflation the losses appear to be additive The trace has been made lighter in portions of the first three prints (Dog No 1) to facilitate photographic reproduction.

and injury effects previously noted for the left ventricular infusion.

The effect of intracavitary carbon dioxide upon the potentials found with right bundle branch block. Two significant differences were observed during insufflation of carbon dioxide after the induction of right bundle branch block. The first difference was that the late potentials of depolarization expanded rather than shrank in recorded voltage when the *right* ventricle was filled with gas (Fig. 4). This was most manifest in the increased amplitude of the right precordial R' on the electrocardiogram or forward enlargement of the whole circular "block" portion of the QRS spatial vector loop in 4 of the 5 instances. In the fifth dog with right bundle branch block, expansion occurred along the left-right axis rather than along the front-back axis (Fig. 5). The second finding was a marked shrinking away of the earliest frontward voltages (i.e., of the initial R of the anterior precordial electrocardiogram) upon filling of the *left* ventricle with carbon dioxide (Figs. 4 and 5).

Discussion

Reduction in the right ventricular epicardial R wave during insufflation of the right ventricular cavity by dielectrics such as gas or mineral oil had been observed by Oppenheimer and associates. They attributed this loss to an insulating effect of the dielectric which shielded the electrode from the *left* ventricle. Comparable conclusions were drawn for the effects on other leads and were tied to the "zone of interference" theory of electrocardiographic genesis of Nahum and Hoff.[10] The zonal theory apparently arose from equating epicardial breakthrough at any ventricular topographic locus with the process of activation of the entire wall at that site. As a result, major electrical contributions at a given instant in the depolarization cycle were attributed to regions of myocardium from which the last vestige of electrical activity was just disappearing. The work of Scher[11] and Durrer[12] leaves little doubt now about the existence of large wave fronts moving generally from endocardium to epicardium during ventricular depolarization. Thus the explanation of changes in peripheral voltage during such further alteration of the already inhomogeneous thoracic volume conductor as provided by insufflation of carbon dioxide must be found by relating the physical distribution of potential in the conductor to the instant-to-instant configuration of the wave fronts of depolarization.

The finding of reduction by right ventricular intracavitary gas in the recorded voltage during normal depolarization and amplification during bundle branch block confirmed the theoretical prediction of Brody[1] and Nelson[3] on the effect of intracavitary blood. As noted in the Appendix, the presence of a nearby mass of decreased resistivity (blood) may be expected to amplify the peripheral effect of radially directed dipoles but to reduce that of tangentially directed dipoles or waves of activation. By contrast, the presence of a nearby mass of increased resistivity (gas) may be expected to reduce the peripheral effect of radial dipoles but exaggerate that of tangential dipoles or of the tangential spread of excitation.

The introduction of carbon dioxide selectively into the ventricular cavities provided a means of dissecting right from left ventricular contributions to the total record of depolarization. Thus, as seen in Fig. 2, in the presence of normal conduction the placing of gas in the right ventricle reduced anteriorly directed contributions *from early in depolarization to moderately* late (note the backward displacement of the later portion of the spatial vector loop); careful comparison between initial and altered precordial lead and loops showed that this loss was continuous from early to late depolarization and not an intermittent loss. Left ventricular filling with gas produced a more drastic loss in middle depolarization; *the fact that the loss was not* greater from "removal" of the greater ventricle may be related to a rapid attenuation of the dielectric effect with increasing distance from the cavity. Thus doublets or waves of activation in the outer shell of the relatively thick-walled left ventricle may have been relatively unaffected by the presence of gas. Although neither right nor left ventricular insufflation was sufficient, the combination of right and left ventricular insufflation of carbon dioxide almost completely removed all anteriorly

directed activity during depolarization. Similarly, when normal early right ventricular depolarization was removed by bundle branch block, left ventricular insufflation sufficed (Fig. 6) to remove the remaining early frontward components—graphically demonstrating the fusion of left septal and right ventricular activation to form the normal right precordial R wave. The ability to remove from consideration right ventricular contributions to the QRS complex should greatly facilitate the more exact assay of the effect of experimental left ventricular myocardial lesions such as those produced by fixation with the injection of formaldehyde.[11]

The fact that the expansion of the voltages of late depolarization in the right bundle branch blocks occurred along the front-back axis of the chest rather than along the left-right axis in all except one animal was somewhat unexpected. Abnormal depolarization of the right ventricular myocardium which resulted from right bundle branch block might have been predicted to be directed largely from left to right if tangential to the right ventricular cavity. However, since the right ven-

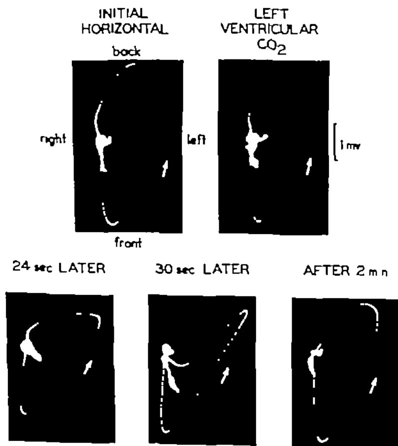


Fig. 3. Serial projections of the horizontal plane vectorcardiogram (lead field system) during insufflation of CO_2 into the left ventricle and subsequently in Dog No. 8. The second record was made just after the peak of lucency and is less drastically reduced than the immediately preceding beat not shown. Note the enlargement of the T loop and the S-T segment shift which developed well after the gas had been expelled from the right ventricle. The QRS loss at the height of ischemia was of posteriorly directed components in the later one third of depolarization in contrast with the immediate lateral loss in middle depolarization when gas was still in the left ventricular chamber. The trace has been made lighter in portions of the prints in this figure to facilitate photographic reproduction.

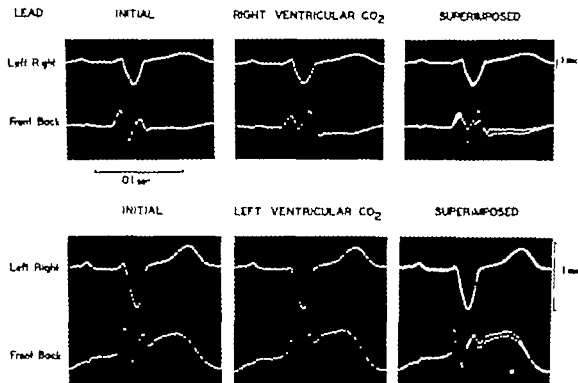


Fig. 4. A comparison of right and left ventricular insufflation of CO_2 in the presence of experimental right bundle branch block in Dog No. 7. In each pair of simultaneous tracings the upper lead is Lead I and the lower lead is the unipolar anterior chest lead presenting the conventional RSR' pattern of RBBB. The top row of prints shows successively the control tracing, the tracing at maximum right ventricular lucency, and the two tracings superimposed. The bottom row shows the control, the maximum left ventricular CO_2 effect, and the two superimposed. Note that gas in the right ventricle resulted in a [illegible] ponded R' but gas in the left ventricle greatly reduced the [illegible].

tricular surface of the canine heart frequently faces slightly to the left as well as ventrally, tangential spread through the right ventricular free wall would thus frequently move toward the front of the chest as well as to the right.

Alternative explanations for the changes in the pattern of depolarization complexes when intracavitary gas was present were considered. An alteration of the membrane potentials which results from change in degree of stretch on the myocardial fibers when contracting against gas rather than blood is a theoretically possible mechanism for deforming the QRS complex acutely. However, alteration of the initial mechanical tension on rat atrium has been reported to produce no detectable changes in the membrane potentials. Anatomic rotation of the heart as a result of either a dilating effect or a shifting of the center of gravity of the heart could account for some of the differences, but no great positional change was actually seen fluoroscopically. A stretching of the right bundle to interfere with conduction might have been considered had the gas been injected under sufficient pressure to produce right ventricular dilatation; however, this possibility was precluded by the observations in which complete right bundle branch block had already been produced. A biochemical alteration from the reaction of carbon dioxide with surface membranes is a possible immediate cause for the change in electrical pattern, but no lag was noted; the maximum electrical effect occurred with maximum fluoroscopic lucency and disappeared when the gross gas disappeared from the ventricle each time.

However, with the left ventricular insufflation another real cause for the development of drastic alterations in the QRS complex and spatial loop became apparent from 15 to 30 seconds *after* the maximum fluoroscopic left ventricular lucency. QRS

deformation occurred accompanied by shifts of the S T segment and ischemic T wave changes Quick removal of the animal from the Trendelenburg position seemed to reduce the subsequent duration of these effects These sequels perhaps attributable to the coronary embolization of gas presented little problem in differentiation from the instantaneous change in peripheral voltages accompanying the peak of left ventricular filling with the gas Both the times of occurrence and the patterns were characteristically different (Fig 3) Oppenheimer and associates[15] instilled gaseous carbon dioxide by fine catheter into a coronary artery without occlusion and without ill effect As contrasted with such benign nonocclusive coronary instillations transient but complete coronary artery occlusions with bubbles of gas (which may by exchange include oxygen and nitrogen in addition to carbon dioxide) seemed the likely cause for the ischemic sequels observed by us

Summary

A reversal of the manifest electrocardiographic effects of the intracavitary blood mass was produced by selectively instilling carbon dioxide into the right ventricle the left ventricle and then both chambers in mongrel dogs In 5 dogs the experiment was

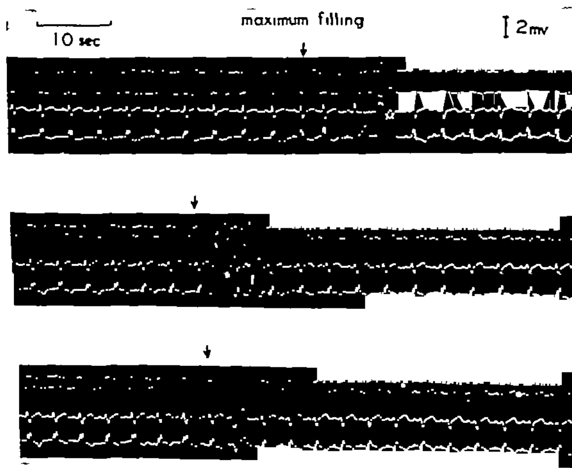


Fig 5 Simultaneous electrocardiograms of Dog N 15 made during right ventricular (*top*) left ventricular (*middle*) and biventricular (*bottom*) insufflation with CO_2—all after the induction of RBBB The leads from above downward in the second and third groups are unipolar back inverted bipolar left right bipolar foot head and bipolar front back In the first group the bipolar left right appears below the inverted unipolar back lead (see Fig 1) Note that left and bilateral ventricular CO_2 greatly reduced the initial R in the front back lead but in contrast to Fig 4 right ventricular CO_2 did not expand the R—although it did expand the S the left right lead The bilateral fillings were not completely simultaneous front back as can be seen by the fact that the left right S expansion follows the initial R loss

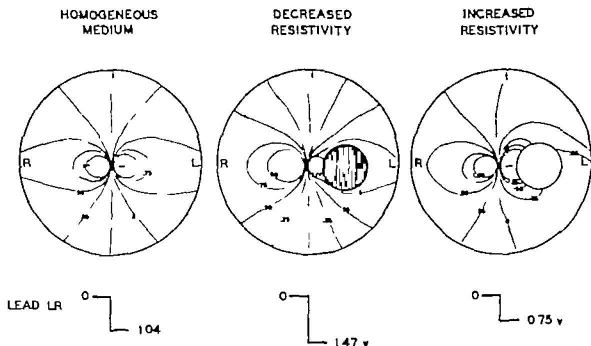


Fig 6 The effect on distribution of potential in a two-dimensional plot of altering cavity resistivity with the axis of the dipole directed radially from the cavity See Appendix for detail

repeated after the percutaneous induction of right bundle branch block

In keeping with the expectation that peripherally recorded voltages generated by dipoles or waves of activation directed radially from the gas filled cavity would be diminished curtailment of the QRS complex and spatial vector loop was found during normal depolarization But in the presence of right bundle branch block the block portions of the tracings increased in peripheral voltage in keeping with the expectation for tangentially oriented dipoles or waves of activation

Insufflation of carbon dioxide into the right ventricular cavity reduced anteriorly directed components in the recordings of surface potentials from moderately early to moderately late in depolarization insufflation of carbon dioxide into the left ventricular cavity reduced laterally directed components especially in middle depolarization Further reduction was noted with bilateral insufflation with especially prominent loss of almost all initial anteriorly directed components Similar loss of both septal and right free wall components of the anterior precordial R occurred during right bundle branch block with left ventricular insufflation

Selective ventricular insufflation with carbon dioxide provides a means of separating in great part right and left ventricular contributions to surface recordings in the dog with an intact chest

Appendix

Fig 6 shows the results of three experiments of mapping isopotential lines and measuring lead voltage in an idealized two dimensional system with conducting paper In each instance a potential drop of 12 volts of direct current was applied to a dipole of 2 pins which were 1 cm apart as designated in the discs The first disc is homogeneous the second has a small circular area of decreased resistivity produced by painting in the area of the circle with conducting silver ink and in the third disc in the same site the circle has been cut out leaving an empty hole or cavity of extreme resistivity

Mapping was made with the exploring pin connected to one post of a direct current voltmeter and the reference pin at point (1) connected to the other post The direction of flow of current between elements of the dipole may be considered to be perpendicular to the isopotential lines The voltage registered in a bipolar surface

lead LR made by connecting the opposing pins to the voltmeter has been represented *diagrammatically below the discs* as though it were impressed on an electrocardiographic record

Note that the good conductor extended the region of high potential a greater distance along the axis of the radial dipole and that thus with the silvered circle the peripheral registration of voltage was enhanced However when the circle was cut out leaving the region highly resistive transfer of high potential along the axis of the radial dipole was impaired by the new boundary and the peripheral registration of voltage was diminished By analogy we may expect intracavitary blood to enhance the surface effect of radial electrical activity [1] and intracavitary carbon dioxide to reduce it

Comparison of Fig 7 and Fig 6 illustrates the reversal of such effects merely by having the dipole oriented in a direction tangential to the boundary of the cavity rather than radial to it Note that now the good conductor reduced the registration of peripheral voltage and the poor conductor increased it

The possibility that the dipole moment itself may be altered by nearby changes in the conducting medium was considered Such an alteration in dipole moment could thus be responsible for the peripheral changes noted To examine this possibility the experiments were carefully repeated with measurement of the interpolar resistance at each step The peripheral results with silvering or cutting out the inner circle were just as before but the change in the interpolar resistance never exceeded 1 1 per cent

We are grateful to Dr Leon Chursey for his review of this manuscript as well as his encouragement and suggestions

REFERENCES

1 Brody D A A theoretical analysis of intracavitary blood mass influence on the heart lead relationship Circulation Res 4 731 1956
2 Brody D A Erb B D and Romans W E The approximate determination of lead vectors and the Burger triangle in normal human subjects Am Heart J 51 10 1956
3 Nelson C V Chatterjee M and Angelakos E T Further studies on the effect of the intracardiac blood on the electrocardiogram Proceedings of the New England Cardiovascular Society 19 7 58
4 Burch G E Abildskov J A and Cronvich J A Studies of the spatial vectorcardiogram in normal man Circulation 7 558 1953

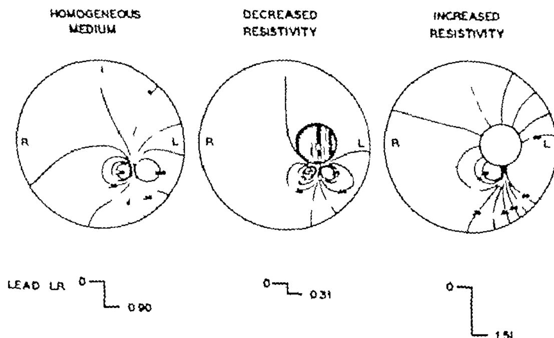


Fig 7 The effect on distribution of potential in two-dimensional plot of altering cavity resistivity with the axis of the dipole tangential to the cavity See Appendix for details.

5 McFee R and Johnston F D Electrocardiographic lead III Synthesis Circulation 9:868 1954
6 Jordan R C and Berwick F W Lead field scalar and loop electrocardiography A preliminary survey on normal adult males and comparison of other method Circulation 18 2-6 1958
Taufic M Ba hour F A and Lew F J Production of heart block in dogs under direct vision S Forum 5 96 1955
8 Oppenheimer M J Long J Durant T M and Wester M R Relation of intra ventricular dielectrics t the unipolar lead Am J Physiol 159 4 6 1949
9 Nahum L H Chernoff H M and Kaufman W Nature of unipolar extremity lead in the dog Am J Physiol 153:529 540 and 547 1948
10 Nahum L H and Hoff H E Nature of the precordial electrocardiogram Am J Physiol 155 215 1948
11 Scher A M and Young A C The pathway of ventricular depolarization in the dog Circulation Res 4:461 1956
12 Durrer D van der Tweel L H Berreklouw S and van der Wey L D Spread of activation in the left ventricular wall of the dog IV Two and three dimensional analysis Am Heart J 49:860 1955
13 Horan L G Burch G E and Cronvich J A The spatial vectorcardiogram in dogs with chronic localized myocardial lesions J Appl Phys 1 15:624 1960
14 Hollander P B and Webb J L Cellular membrane potential and contractility of normal rat atrium and the effects of temperature tension and stimulus frequency Circulation Res 3 604 1955
15 Oppenheimer M J Stauffer H M Schoff L A and Durant T M Physiological effects of carbon dioxide gas introduced into coronary arteries Am J Physiol 196 1308 1959

Vascular lesions in experimental pulmonary embolism

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The experimental production of pulmonary vascular lesions has received growing attention since 1948, when Harrison[1] published his results on heterologous clot embolism in rabbits. Numerous reports have since appeared, based on experiments with different species of animals and a great variety of methods. The lesions described differ in detail according to the species and the techniques used, but disregarding those differences, most published results can be summarized as shown in Table I. It can be seen from this table that although all lesions can appear as the effect of pulmonary hypertension, some of them may also result from different mechanisms, such as multiple pulmonary embolism or hypersensitivity.

The application of these observations to human subjects with pulmonary vascular lesions raises the question of separating the effects of pulmonary hypertension from those of other injurious agents and especially from those of multiple embolism. Thus one can find in the literature cases of pulmonary arteritis attributed to pulmonary hypertension, to multiple embolism, to hypersensitivity, to rheumatic fever, or to a combination of these factors. Many of the papers on multiple embolism produced by blood clots contain no information on pulmonary arterial pressure. On the other hand, Thomas and O'Neal produced chronic blockage of the pulmonary circulation by means of multiple emboli of plastic beads that resulted in dilatation and hypertrophy of the right ventricle (used by these authors as proof of pulmonary hypertension) without vascular lesions in the lungs.

On the basis of the data previously mentioned, an experimental situation was planned in which the anatomic effects of pulmonary hypertension could be clearly separated from the effects of multiple

*Table I. Pathogenesis of experimental pulmonary vascular lesions**

Lesion	*Pathogenesis*
Intimal thickening	Multiple thrombi embolism Pulmonary hypertension
Medial hypertrophy	Pulmonary hypertension
Muscularization of the arteriolar media	Pulmonary hypertension
Plexiform or angiomatoid lesions	Multiple thrombi embolism (?) Pulmonary hypertension (?)
Arteritis or arteriolitis with or without necrosis	Multiple thrombi embolism Cotton embolism Hypersensitivity Pulmonary hypertension

*For bibliography see Reference 2.

From the Pathology Unit, National University School of Medicine, Mexico City, Mexico.
Received for publication Aug. 8, 1960.

Table II *Distribution of animals*

Group	Number of animals	Emboli	Site of injection	Schedule of injection	Sacrifice time	Purpose
A	6	Fibrin clots	Left pulmonary artery	5 injections at 2 week intervals	15 days after the last injection	Fibrin effect on the vascular wall eliminating the possible effect of pulmonary hypertension
B	6	Fibrin clots	Peripheral vein	5 injections at 2 week intervals	15 days after the last injection	
C	6	Plastic beads	Left pulmonary artery	5 injections at 2 week intervals	15 days after the last injection	Effect of the possible pulmonary hypertension without fibrin or blood
D	6	Plastic beads	Peripheral vein	5 injections at 2 week intervals	15 days after the last injection	
E	6	Whole blood clots	Left pulmonary artery	Weekly injections for 5 weeks	7 days after the last injection	Effect of whole blood on the vascular wall separating the possible effect of pulmonary hypertension
F	7	Whole blood clots	Left pulmonary artery	1 injection	2 4 20 36 48 and 72 hours after the injection	Early stages of the evolution of the embolic pulmonary vascular lesions

emboli The aim of this paper is to report the results obtained in a series of experiments in which multiple unilateral pulmonary embolism was produced in dogs with autologous whole blood clots autologous fibrin and inert plastic beads The dog was chosen for these experiments because it has been shown that in this animal pure sustained pulmonary hypertension can produce vascular lesions and because cardiac catheterization can be easily performed

Material and methods

1 Animals Thirty seven young mongrel dogs of both sexes were used Their average weight was 40 pounds They were kept in separate cages throughout the experiments and were fed a standard diet The 37 dogs were divided into 6 groups each receiving a different treatment according to Table II

2 Preparation of emboli Three types of emboli were utilized fibrin clots whole blood clots and plastic beads

FIBRIN CLOTS The technique used for the preparation of fibrin clots was essentially that of Barnard

BLOOD CLOTS Twenty milliliters of whole blood was allowed to clot in a test tube The clot was finely cut until the fragments passed easily through a No 18 gauge needle suspended in saline and injected through the catheter

PLASTIC BEADS Lucite plastic beads 50 to 150μ in diameter were injected according to the technique used by Thomas and O Neil[4] The amount of plastic beads injected was equivalent in volume to two thirds of the clots which was thought to result in approximately the same degree of obstruction to the pulmonary circulation as that produced by either whole blood or fibrin clots

3 Catheterization technique In Groups A C E and F unilateral pulmonary embolism was carried out by means of cardiac catheterization The animals were anesthetized with intravenous pentobarbital (35 mg/Kg of weight) Each of the branches as well as the main trunk of the external jugular vein on each side was used for one catheterization allowing therefore

*Obtained through the courtesy of Du Pont de Nemours W ilmington Del.



Fig 1 Organized thrombus in the lumen of large pulmonary artery The intima is thickened probably as the result of previous embolization Aldehyde fuchsin and Van Gieson ×200

six possibilities for catheterization of each dog When thrombosis or cicatrization did not allow completion of five catheterizations at the level of the neck the axillary vein was used Under fluoroscopic guidance a No 8 Cournand catheter was introduced into the left branch of the pulmonary artery Blood clots or plastic beads were then slowly injected followed by 10 ml of saline solution to wash the catheter Animals of all groups except those of Group F were injected during the following three days with 150 000 units of procaine penicillin every 12 hours

4 Handling of the lungs Animals were sacrificed by rapid intravenous injection of 500 mg of Kemithal Complete autopsies were performed The heart and lungs were separated together from the thoracic cavity and fixed by intratracheal injection of 10 per cent formalin they were kept in containers with the same fixative

Representative (2 to 8) sections were taken from each lobe of the left lung and from the right lower lobe They were embedded in paraffin sectioned and stained with hematoxylin eosin Gomori s fuchsin paraldehyde for elastic fibers and Foot s stain for reticulum and collagen

Results

Autopsies of the sacrificed animals did not reveal macroscopic alterations either in the lungs or in the heart The right ventricular and auricular walls of the heart were carefully examined and measured and no differences were found from hearts of normal animals However a definite decision in this respect is not easy since there were wide variations in breed and weight The histologic changes are discussed first and their distribution in the different groups of animals is then presented

Microscopic changes The microscopic lesions found were (1) blood clots at various stages of organization in the lumen of the arteries (2) vacuolation of the endothelial cells that were in direct contact with the clots and (3) arteriolitis In the following paragraphs each one of these lesions is described and their distribution



Fig 2 Polypoid formation in medium-sized artery Aldehyde fuchsin and Van Gieson ×180



Fig 3 Focal fibr timal thickening f large pulmonary artery Verhoeff Van Gieson X230

in the different groups of animals is examined

BLOOD CLOTS Blood clot emboli were found especially in vessels that were over 100μ in diameter always with a well individualized external elastic membrane and in the vicinity of bronchi or bronchioles Most thrombi were in an advanced stage of organization with deposits of connective tissue and vascular neoformation (Figs 1 and 2) Other than the endothelial vacuolation which is discussed below only occasional lesions were found in the wall of the vessels in two of them coinciding with the site of implantation of the thrombus there was destruction of the elastic membrane and substitution of the media by connective tissue which continued the connective tissue of the organized clot (Fig 3) Focal fibrotic thickening of the intima was rarely found and probably corresponded to well organized and endothelial covered clots (Fig 4)

ENDOTHELIAL VACUOLATION This was a constant finding although of variable intensity The endothelial cells in intimate contact with the clot had a swollen aspect the cytoplasm being occupied by a large vacuole unstained with the techniques used The nuclei had a peripheral position simulating signet ring cells (Fig 5) Elastic fiber stains showed clearly that the alteration was under the limiting internal membrane (Fig 6) In most of the involved vessels the endothelium beyond the implantation site of thrombi had a normal aspect in addition most thrombi were of recent formation *A organization ad vanced endothelial vacuolation became less apparent or was absent Vessels of the same or larger diameter without thrombi showed a normal endothelium

ARTERIOLITIS The term arteriole is used throughout this paper in reference to vessels of small diameter usually less than 50μ situated away from bronchi or bronchioles with only one internal elastic membrane and without muscular coat Foci of inflammatory infiltration formed by polymorphonuclear leukocytes lymphocytes and macrophages mixed with variable amounts of erythrocytes were found



Fig 4 Embolus implanted in medium sized artery with destruction of elastic and muscular fibers Note absence of inflammat Aldehyde fuchsin and Van Gieson X180



Fig. 5. Recent thrombus in medium sized artery. Endothelial cells in the top are swollen, vacuolated and contain slightly basophilic material. Hematoxylin eosin. X230.

only in the alveoli immediately surrounding the arterioles (Fig. 7). Transverse sections of arterioles showed that inflammatory cells surrounded the vessels in cuff-like fashion (Fig. 8). Within the groups of inflammatory cells small clefts filled with red blood cells were seen suggesting capillary proliferation; stains for reticulum fibers, however, showed that they had neither wall nor endothelial lining (Fig. 9). The arteriolar wall had a normal appearance; special stains revealed integrity of the elastic fibers (Fig. 10); rupture or alterations of the wall were not seen in any case. The observation of numerous sections revealed that there was a tendency for accumulation of inflammatory cells at the sites of arteriolar bifurcation (Fig. 11).

Distribution of microscopic changes in the different groups. In Group A, arteriolitis was found in all sections of the left lung, predominantly in the lower lobe. No alterations were seen in the right lung. In Group B, arteriolitis was found in both lungs in all animals, but the changes were few and small and many sections had to be studied before the lesions were identified with certainty (Table III). Groups C and D, which received multiple plastic bead emboli by way of the left pulmonary artery and by a systemic vein, respectively, showed no lesions of any kind. Finally, the results obtained in animals of Group E, to which autologous blood clots were given through the left pulmonary artery, are summarized in Table IV. It can be seen from this table that arteriolitis was predominant in the lower lobes and that it was present despite the lack of organized thrombi in larger arteries. In Dog No. 4, vascular lesions in the right lung were interpreted as being caused by reflux of clots in one or more of the embolizations; the same alterations were found in the left lung. In the other animals belonging to this group no lesions were found in the right lung.

Animals of Group F received a single autologous thrombus embolization in the left lung and were sacrificed at intervals that varied between 0 and 72 hours after emboli-



Fig. 6. Partially organized thrombus in a large pulmonary artery, showing marked vacuolation of endothelial cells. Aldehyde fuchsin and Van Gieson. X250.

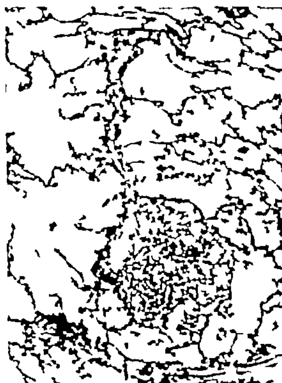


Fig 7 Arteriolitis formed by lymphocytes macrophages and scarce polymorphonuclear leukocytes there are few red blood cells between the inflammatory elements The wall of the arteriole is normal Hematoxylin-eosin ×180

zation The microscopic findings are summarized in Table V It can be seen that vacuolation of endothelial cells and arteriolitis appeared at 24 hours and persisted to the last observation made 72 hours after embolization A striking feature was that in the periarteriolar inflammatory nodules more well preserved erythrocytes were found among the cells than in similar lesions from animals of other groups

Discussion

The results obtained in the present experiments indicate that repeated fibrin emboli or complete autologous blood emboli when introduced into the peripheral veins or into the left pulmonary artery produced several types of lesions in the pulmonary vessels in the dog When the clots are made of whole blood thrombi in different stages of organization are found in pulmonary vessels over 100μ in diameter Focal fibrous thickening seen in some arteries of similar caliber may also be considered to be the result of organization and retraction of a clot that later on is covered by endothelium[6,7] Only in two instances were lesions with destruction of the elastic fibers in the media of these vessels observed and these were associated with organized thrombi Lesions of the same type have been described in rabbits by Heard[8] and in rabbits and mice by Barnard Another type of lesion related to whole blood embolization is endothelial vacuolation as first shown in the dog by Jacques and Hyman[9] Undoubtedly this type of endothelial alteration is related to the presence of clots but its nature is

Table III Results in Groups A and B

Animal number	*Group A*	*Group B*
1	\	\
2	\	\
3	\	\
4	+	\
5	\	\
6	+	\

+ Died during the experiment
\ Arteriolitis

Table IV Results in Group E

Animal number	*Right lung*	*Left lung*		
		U L	*Lingula*	*L L*
1	0	0	\	\
2	0	+0	+\	\
3	0	\	+\	+
4	+\	\	\	+\
5		–		
6	0	+	\	\

0 No l[illegible]
+ O[illegible] and thrombi in l[illegible]
\ Arteriolitis in small arteries and arterioles
\ E[illegible] and intense arteriolitis

Table V Results in Group F

Sacrificed at	*Right lung*	*Left lung*
2 hr	0	0
4 hr	0	+
20 hr	0	+
24 hr	0	+\
36 hr	0	+\
48 hr	0	+\
72 hr	0	+\

0 No lesions
+ Re[illegible] thrombi in th[illegible] of large [illegible]
\ Arteriolitis



Fig. 8 A cross section of arteriolitis showing the cuff-like arrangement of the infiltrate. Aldehyde fuchsin and Van Gieson ×180

unknown and its significance in the further evolution of the lesions was not explored in these studies.

The arteriolitis found in these experiments might be due to three theoretical possibilities: pulmonary hypertension, hypersensitivity, and the effect of fibrin on the vascular wall. Although no direct measurements of pulmonary pressure were made in this study, the first possibility appears unlikely because of the following data. (1) In the animals receiving unilateral fibrin or whole blood clots (Groups A and E), arteriolitis was seen only in the embolized side. (2) In one animal in which arteriolar lesions were seen in both lungs (Dog No. 4 of Group E), proof was found that clotted blood emboli had passed to the opposite lung. (3) If there was pulmonary hypertension, it must have been low and or transient because the right side of the heart did not show dilatation or hypertrophy and the blood vessels did not have lesions that could be attributed with certainty to hypertension such as arterial medial hypertrophy or the presence of a muscular media in the arterioles.[9,12] Furthermore, Jacques and Hyman[9] measured pulmonary arterial pressure in dogs which received 10 intravenous injections of blood clots and found discrete and transitory elevations of pressure. (4) Finally, no vascular lesions were found in those dogs in which pulmonary circulation was obstructed by injections of plastic beads. For all these reasons it may be concluded that if it ever existed, pulmonary hypertension did not represent a pathogenic factor in the production of arteriolitis.

Hypersensitivity is capable of producing acute inflammation of arteries and arterioles in many parts of the organism including the lung. Two main reasons may be advanced in opposition to the idea that hypersensitivity could have played an important role in the production of arteritis as described in the present experiments. (1) Besides affecting arterioles, hypersensitivity also involves larger vessels that have a muscular media and produces necrosis and destruction of the wall; this was not found in the present material.



Fig. 9 The lumina of alveoli occupied by the inflammatory infiltrate of arteriolitis. Note the absence of vascular neoformation. Foot stain ×150



Fig 10 The integrity of the arteriolar wall in the area of inflammation can be demonstrated with elastic stains Aldehyde fuchsin and Van Gieson ×150

(2) Lesions were found 24 hours after embolization in those animals which had not received emboli previously a finding which speaks against a hypersensitivity mechanism that requires a longer time for the formation of specific antibodies

The data indicate that a factor residing in fibrin is responsible for the arteriolitis Thus the lesions appeared only in those animals with fibrin or whole blood embolism arteriolitis was found only in vessels of the lung that had received this type of emboli It must be kept in mind that acute arteriolitis was found away from organized thrombi and that neither the lumen nor the arteriolar wall showed any alterations furthermore in animals which were sacrificed 24 to 72 hours after a single embolization with blood clots the inflammatory lesions showed a larger number of well preserved erythrocytes than did those in dogs examined 1 or 2 weeks after the last embolization These data suggest that arteriolar damage is accompanied by an increase in arteriolar permeability with focal hemorrhage and that the accumulation of inflammatory cells can be due at least in part to this hemorrhage The fibrin factor responsible for arteriolitis would act only on those vessels in which it might have adequate concentration

The preferential localization of arteriolitis at the sites of bifurcation of these vessels call to mind Arias Stella's description[8] of the so called plexiform or angiomatoid lesions found in primary pulmonary hypertension in man[15] Evans[16] thought that capillary proliferation in the vicinity of an artery was due to a congenital defect in the elastica but Arias Stella showed by means of serial sections that the alteration is localized at the sites at which arteries give off much smaller vessels or arterioles These studies have been confirmed by Wagenvoort[17] The nature of the lesion herein described is different however since in this case foci of inflammatory cells are seen within the alveoli and around the arterioles whereas in human primary pulmonary hypertension glomeruli are formed by proliferation of capillaries within the arteriolar lumen

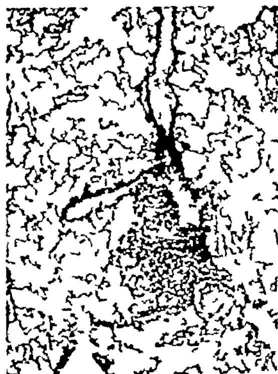


Fig 11 Arteriolitis localized at the bifurcation of the blood vessel Aldehyde fuchsin and Van Gieson ×150

This study was planned to aid in the interpretation of human pulmonary vascular lesions. If the findings in the dog can be extrapolated to human beings then the results show that intimal thickening of arteries and arterioles as well as arteriolitis can be the consequence of embolism without the participation of hypertension or hypersensitivity. Therefore even when functional and/or anatomic reasons would exist in a given case to assure the existence of pulmonary hypertension the finding of lesions similar to those herein described suggests the need for a search for possible sources of emboli.

Summary

Numerous experimental studies have shown that it is possible to produce pulmonary vascular lesions by different methods. Two of the most effective methods are (a) multiple embolization with blood clots and (b) pulmonary hypertension produced by shunting systemic flow into the pulmonary artery or into one of its branches. Since many studies have failed to separate the effects of multiple emboli from those of pulmonary hypertension a series of experiments were planned in which unilateral multiple pulmonary embolism was produced by injecting autologous fibrin clots in one group of animals autologous whole blood clots in a second group and plastic bead emboli in a third group of dogs. Appropriate controls received the emboli through a peripheral vein whereas the experimental animals were embolized through a catheter introduced into the left pulmonary artery. Another group of animals received a single embolization of whole blood clots into the left pulmonary artery and were sacrificed at intervals varying between 0 and 72 hours. The results were that in all animals which received fibrin or clotted blood emboli the three following types of pulmonary vascular lesions were found (a) organized or partially organized clots in the lumen of arteries with minimal lesions in the wall with the exception of (b) a peculiar vacuolated aspect of the endothelium that was in intimate contact with the clots and (c) peripheral arteriolitis without alteration in the arteriolar wall accompanied by focal hemorrhage usually localized at the branching sites of vessels. These lesions appeared 24 hours after the injection of emboli. No anatomic traces of pulmonary hypertension were found. No anatomic changes were seen in those instances in which plastic beads were given.

The results are discussed and it is pointed out that whereas organized thrombi and endothelial vacuolation are due to the presence of the embolus arteriolitis is probably the result of a fibrin factor. Pulmonary hypertension and hypersensitivity can be discarded as causal agents of the vascular lesions found in these experiments.

REFERENCES

1. Harrison C V Experimental pulmonary arteriosclerosis J Path Bact 60 289 1948
2. Pérez Tamayo R Arteriosclerosis pulmonar Revisión del significado de estudios experimentales recientes en la patogenia de las lesiones humanas Principia Cardiol 6 12 1959
3. Perez Tamayo R and Brandt H Lesiones vasculares de la hipertension pulmonar Temas de Patologia del Torax libro homenaje al Dr Alejandro Celis Mexico D F 1959 Ed Mendez-Oteo
4. Thomas W A O'Neal R M and Lee K T Experimental pulmonary hypertension and arteriosclerosis absence of intimal reaction in pulmonary arteries of rabbits with right ventricular hypertrophy following pulmonary vascular obstruction by nonthrombotic material (plastic beads A M A Arch Path 62:56 1956
5. Barnard P J Experimental fibrin thromboembolism of the lungs J Path Bact 65 129 1953
6. Wartman W B Jennings R B and Hudson B Experimental arterial disease I Reaction of the pulmonary artery to minute emboli of blood clot Circulation 4 747 1951
7. Harrison C V Experimental pulmonary hypertension J Path Bact 63 195 1951
8. Heard B E Experimental study of thickening of pulmonary arteries of rabbits produced by organization of fibrin, J Path Bact 64 13 1952
9. Jacques W E and Hyman A L Experimental pulmonary embolism in dogs A M A Arch Path 64:487 1958
10. Mueller W H Dammann J F and Head W H Changes in the pulmonary vessels produced by experimental pulmonary hypertension Surgery 34:363 1953
11. Ferguson D J Berkas E M and Varco R L Circulatory factors contributing to alterations in pulmonary vascular histology S Forum 4:267 1953
12. Dammann J F Smith R T and Mueller W H J The experimental production of pulmonary vascular disease S Forum 6 155 1955
13. Arias-Stella J Hipertension pulmonar pri

Table I Data on subjects and platform and acceleration and force values

Subject	Age (yr)	Height (cm)	B S A (M²)	Weight of subject (grams × 10³)	Platform weight (grams × 10³)	Subject + platform weight (grams × 10³)	I J p (m/sec)	I J exp (force-grams)	I J asp (m/sec)	I J asb (force-grams)
I	(4)	168 9	1 65	60 000	5 909	95 909	3 21	281 59	4 5	394 6
D B	(23)	157 9	1 91	71 363	25 909	97 272	4 25	472 14	5 0	496 64
T	(15)	174	1 78	66 136	5 909	92 045	5 18	496 97	5 73	538 57
L C	(31)	187 2	2 07	82 272	25 909	108 181	3 5	386 64	4	574
\	(26)	195 6	2 37	106 818	25 909	132 727	3 0	406 99	3 5	474 36
D L	(24)	174	1 81	68 181	25 909	94 090	3 0	298 71	4 0	391 04
A S D	(23)	174	1 80	67 272	25 909	93 181	3 5	309 24	4 25	404 39
F T	(4)	169	1 65	57 727	25 909	83 636	3 0	256 2	4 5	84 3
W J H	(34)	165	1 54	50 909	25 909	6 819	2 7	211 9	3 3	258 86
J A K	(25)	177	1 82	66 818	5 909	92 7 7	3 0	284 1	3 6	340 87
P	(4)	17	2 08	96 818	25 909	122 7	2 7	338 37	3 0	375 96
L P	( )	182	1 93	73 363	25 909	99 272	3 68	373 04	4 95	501 75
D M	(24)	190	2 03	85 000	25 909	110 909	2 4	271 8	3 7	30 78
R C	(31)	1 9	1 95	77 273	25 909	103 18	3 3	347 7	4 05	476 72
G S	(23)	173	1 84	71 818	25 909	97 727	2 7	269 44	3 45	343 8
R T	(24)	177 5	1 98	81 818	25 909	107 727	2 7	297 01	4 5	495 0
B G T	(31)	1 0 6	1 82	72 045	25 909	97 954	9	390 09	4 8	490 12
J C F	(24)	177 5	1 94	77 272	25 909	103 181	4	442 52	5 4	568 95
H R	(8)	185 4	2 05	79 091	25 909	105 000	4 75	455 65	6 24	609 04
A D M	(29)	1 9	1 93	68 181	25 909	94 090	3 69	354 53	5 31	510 18
T B	(23)	169	1 68	60 454	25 909	86 363	5 74	506 2	7 04	670 85
C	(25)	177 7	1 90	68 181	5 909	94 090	3 91	375 67	5 48	5 6 5
G M	(23)	182 9	1 82	63 636	25 909	89 545	4 0	365 75	5 8	530 3
Ra	(22)	177 8	1 94	77 272	5 909	103 181	4 4	461 59	4 98	524 7
B	(3)	180 3	2 07	84 091	25 909	110 000	2 14	240 37	3 43	385 27
Average	(25)	176 85	1 88	73 357	———	99 261	3 51	353 01	4 57	455 96
Standard deviation	(1) ±3 9	±6 56	±0 17	±12 177	———	±12 177	±0 86	±81 22	±1 07	±99 2

*Values of [illegible] subjects [illegible] average and standard deviation [illegible] all factors (excepting platform weight) age [illegible] (average 25 standard deviation ± 3 9) height (176 85 cm ± 6 56) body surface area (1 88 sq meters ± 0 17) subject weight (73,357 kg ± 12 177) subject plus platform weight (99 261 kg ± 12 177) I J [illegible] (3 51 cm/sec ± 0 86) I J [illegible] force (353 01 grams ± 81 2) I J [illegible] (4 57 cm/sec ± 1 07) I J [illegible] force (455 96 grams ± 99 2)

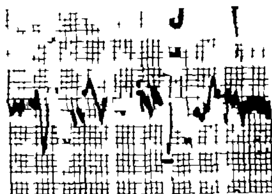


Fig 1 Acceleration record suspended mid respiration Normal male subject aged 25 years weight 154 pound height 67 25 inches Calibration 14 0 small vertical spaces = 1 0 mv = 3 0 cm /sec I J wave = 1/14 × 3 0 = 4 5 cm /sec

Direct measurements of the I J stroke acceleration value (calibration 1 0 millivolt output = 3 0 cm /sec) were made on expiratory and inspiratory records of a stable pattern from complex to complex The force value was calculated for expiration and inspiration by the classic formula

$$F = \frac{M \quad A}{G}$$

with all measurements in the centimeter gram second system The force (F) was in grams the body plus platform mass (M) in grams the acceleration (A) in cm /sec ² and the gravitational constant (G) for this geographic location is 979 3 cm /sec ²

Complete data on subjects and platform and acceleration (cm /sec ²) and force (grams) values are given in Table I An acceleration record (suspended mid respiration) for a normal subject is shown in Fig 1

Discussion

Fig 2 shows the frequency distribution of subject data with one standard deviation for age (*A* years) height (*B* centimeters) body surface area (*C* square meters) and body plus platform weight (*D* kilograms) Fig 3 shows the frequency distribution with one standard deviation of the expiratory I J acceleration (*A* cm /sec ²) and calculated force (*B* grams) values and the inspiratory I J acceleration (*C* cm /sec ²) and calculated force (*D* grams) values

There are a few published values of quantitative acceleration measurements from ultralow frequency systems to compare with values of this report The mean I J acceleration value given by Scarborough and associates[13] (25 male subjects 20 29 years old) from a differential pendulum is 5 93 mg Conversion (1 0 mg = 0 98 cm /sec) gives a value of 5 81 cm sec ² Hollis obtained a mean I J value of 5 01 cm /sec ² from a simple pendulum[7] and 4 42 cm /sec from a ball bearing bed[8] ballistocardiograph

The mean value (average expiration plus average inspiration I J/2) of the present study with Nickerson type of spring ultralow frequency system is 4 04 cm sec ² This value is lower than the others because of the heavy platform (25 909 grams) of the Nickerson type of ultralow frequency system

It is of interest to compare these mean acceleration values with the theoretically predicted quantitative acceleration (force) value as determined by Noordergraaf and Heynekamp In Fig 2 of their article[14] the amplitude of the I J stroke is given in dynes This value (280 000 dynes) may be converted to cm sec by division with the average total mass of body and ballistic platform (75 000 grams) as given by Noordergraaf and Heynekamp[14] A resultant value of 3 73 cm sec is obtained The closeness of this value to the experimentally determined values is quite good considering that the theoretical analysis of Noordergraaf and Heynekamp[14] is free of the mechanical factor of resonance amplification present in all ballistic systems

Since the acceleration values given above are influenced by the mass of the ballistic platform which increases inertial impedance to acceleration a more exact comparison of these values would necessitate correction for this factor Use of the mean subject weight and the mean subject plus platform weight for each value given above results in the following corrected acceleration values (1) Scarborough and associates differential pendulum 6 33 cm /sec ² (2) Hollis[7] simple pendulum

*Corrected amplitude = measured amplitude times body + platform [illegible] platform/body weight

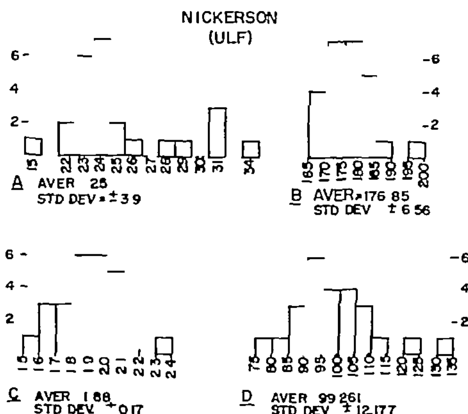


Fig. 2. Bar frequency diagrams showing number of subjects with average and one standard deviation for A, age in years; B, height in centimeters (group units of 5.0 cm.); C, body surface area in square meters (group units of 0.1 sq. meter); D, combined weight factor body plus platform in kilograms (group units of 10 kilograms).

6.00 cm./sec.; (3) Hollis' ball bearing bed, 5.29 cm./sec.; and (4) present study, 5.47 cm./sec.[2] These results show the best correlation between the differential pendulum and the simple pendulum, but all results are improved in reference to the differential pendulum. Correction of Noordergraaf and Heynekamp's[4] theoretical value assuming a platform mass of 5,000 grams gives 4.00 cm./sec. as the adjusted value. It is the least improved in reference to the differential pendulum, most likely due to the reason given previously in addition to smallness of the assumed value for platform weight.

A similar comparison of mean force values of normal subjects from different systems is of interest. The mean force value from a differential pendulum[12] (25 male subjects 20-29 years old) is 485.8 grams. Hollis has given a similar value of 435.24 grams from a simple pendulum and 397.38 grams from a ball bearing bed[8] ballistocardiograph. The mean force value (average expiration plus average inspiration I J/2) of the present study is 405.99 grams. An average value determined from data given by Von Wittern[13] (4 subjects, simple pendulum) is 365 grams. Conversion of the theoretical force value (280,000 dynes) of Noordergraaf and Heynekamp[14] gives a value of 285.7 grams. The lowness of this last value is likely due to factors already mentioned in a discussion of the acceleration values. Calculation of the "true" unloaded force value by multiplying the corrected mean acceleration value by the mean subject weight for each system did not result in any significant improvement except for the value from the simple pendulum used by Hollis, i.e., an increase of 14.3 grams. The lack of improvement in corrected values is explained by the greater mass (subject plus platform) used when calculating force from the uncorrected directly measured platform acceleration.

Although not strictly comparable because of differences in characteristics of

the systems it is of interest to note the force value obtained for normal subjects from a spring type of high frequency platform Starr[14] obtained a mean (expiration plus inspiration/2) value of 413 grams (range 406-420) for healthy young male adults This is a reasonably good agreement with the force values obtained by the ultralow frequency technique An average value obtained from the five mean ultralow frequency values given previously is 417 88 grams The closeness of this average value to Starr s high frequency platform value is significant

At present it would appear as has been stated [7] that the differential pendulum[18] is the most efficient system to date for obtaining the acceleration force values of the ultralow frequency ballistocardiogram

Summary

1 The acceleration force values of 25 normal male subjects from a Nickerson type of ultralow frequency ballistocardiographic system have been given

2 The resultant mean values have been compared to values from other ultralow frequency systems and theoretically corrected acceleration values have been calculated for each system

3 The force value for normal subjects from a spring type of high frequency system has been compared to an average mean value obtained from force data of five ex

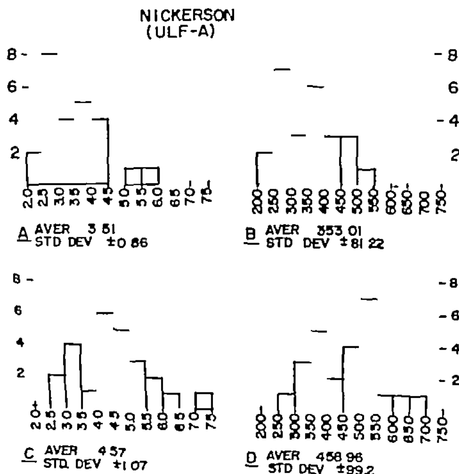


Fig 3 Bar frequency diagrams showing number of subjects with average and one standard deviation for A expiratory I J acceleration in group unit of 0 5 cm /sec (average 3 51 standard deviation ± 0 86) B expiratory I J force in group units of 50 grams (353 01 ± 81 22) C inspiratory I J acceleration in group units of 0 5 cm /sec (4 57 ± 1 07) and D inspiratory I J force in group units of 50 grams (458 96 ± 99 2)

perimental studies using the ultralow frequency technique The closeness of the two values is remarkable

4 It appears that the most efficient and sensitive of the ultralow frequency systems is the differential pendulum

REFERENCES

1 Jonnart L Étude du balistocardiogramme humain I Technique Acta cardiol 7:432 1952
2 Scarborough W R and Talbot S A Proposals for ballistocardiographic nomenclature and conventions revised and extended report of committee on ballistocardiographic terminology Circulation 14 435 450 1956
3 Jonnart L and Ghys A Étude d balisto cardiogramme humain II Le balistocardiogramme d acceleration Acta cardiol 8 232 1953
4 Jonnart L and LeQuime J Nouvelle methode balistocardiographique Arch mal coeur 46 752 1953
5 Nickerson J L and Curtis H J The design of the ballistocardiograph Am J Physiol 142 1 1944
6 Hollis W J Observations on the ballistocardiogram from pendulum spring and ball bearing platform and a direct body air mattress upport system Exper Med & Surg 14 299 1956
7 Hollis W J The systolic I J acceleration force alues of 51 normal male subjects from an ultralow frequency pendulum ballistocardiographic system Am Heart J 57 730 1959
8 Hollis W J Observations on the systolic I J stroke acceleration force lues of 49 male subjects from a roller ball bearing ballistocardiographic bed Am Heart J 57 738 1959
9 Starr I Studies made by simulating systole t necropsy XII Estimation of the initial cardiac forces from the ballistocardiogram Circulation 20 74 1959
10 Smith J I A calibrated bar magnet velocity meter for use in ballistocardiography Am Heart J 44 872 1952
11 Perls T A and Kissinger C W An integrating and differentiating bar magnet elocity meter for use in ballistocardiography Rev Sci Instruments 25:983 1954
12 Marks L S Mechanical engineer handbook ed 4 New York 1941 McGraw Hill Book C p 84
13 Scarborough W R Folk F F III Smith P M and Condon J H The nature of records from ultralow frequency ballistocardiographic systems and their relation to circulatory events Am J Cardiol 2 613 1958
14 Noordergraaf A and Heynekamp C E Genesis of the human longitudinal ballistocardiogram from the changing blood distribution Am J Cardiol 2 748 1958
15 Von Wittern W W Force ballistocardiography WADC Technical Report 52 340 November 1952 p 10
16 Starr I Normal standard for amplitude of ballistocardiograms calibrated by force Circulation 11:914 1955

Cardiovascular and antiarrhythmic activity of amotriphene

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Recent clinical and experimental studies have indicated that amotriphene possesses interesting and important therapeutic properties for the treatment of angina pectoris and mild cardiac arrhythmias. Karczmar, Bourgault, and Elpern have reported a significant cardiac antiaccelerator activity in the epinephrine-driven rabbit heart and an in vitro coronary dilator activity two to three times that of papaverine. Bobb and Green have reported significant in vivo coronary dilator activity in the dog, and Farah and Birnbaum have reported antiarrhythmic properties in the isolated rabbit auricles and in the intact dog that were approximately 4 and 8 times as effective as those of quinidine and Pronestyl, respectively. Page and Sasse[4] have reported an increase in coronary sinus oxygen saturation in dogs. Introductory clinical studies by Harris[5] indicate that this drug is effective in the treatment of angina as well as cardiac arrhythmias of both atrial and ventricular origin. The present study is a report of further laboratory studies on the cardiovascular activity and toxicity of this compound.

Methods

Experimental studies were conducted under a variety of procedures. The basic experimental technique used dogs anesthetized with pentobarbital, 30 mg./Kg. intravenously, and maintained on artificial respiration with room air. Arterial blood pressure was measured with a Statham transducer from the femoral artery. Heart contractile force was measured with a Walton strain gauge attached to the surface of the right ventricle. Both parameters were recorded with a Grass oscillograph. Electrocardiograms (ECG—Lead II) were taken throughout the experiments. In some instances the other bipolar and unipolar leads were also recorded. Amotriphene was administered intravenously into the femoral vein.

Experiments in 19 dogs were carried out by means of this procedure. Eleven other experiments were conducted in dogs pretreated with morphine, 10 mg./Kg. subcutaneously, and pentobarbital, 15 mg./Kg. intravenously, followed by penthienate bromide, 0.5 mg./Kg. subcutaneously. The latter drug, a parasympatholytic, produces

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Myordil, 3-dimethylamino-1,1,2-tris-(4-methoxyphenyl)-1-propene hydrochloride (WIN 5494), registered trademark, available from Winthrop Laboratories Inc., New York, N. Y.

a sustained sinus tachycardia within 15 minutes after administration

Eighteen experiments were conducted in dogs administered sublethal doses of digitalis using ouabain digitoxin U S P or digitalis tincture U S P Each digitalis preparation was administered intravenously in divided doses or by slow continuous infusion in an amount equaling an ultimate dosage of 0 5 to 1 02 cat units per kilogram equivalent to milligram units previously published [6] The establishment of a ventricular ectopic tachycardia single or multifocal of at least 10 minutes duration was the criterion of digitalis toxicity Amotriphene was administered intravenously in increments of 2 0 mg /Kg at 5 minute intervals until the arrhythmia was converted to a normal sinus rhythm or until heart block occurred

Two experiments were conducted in chemically sympathectomized dogs using the procedure of Brewster Bunker and Beecher [7]

ECG toxicity studies were conducted in 26 cats using the U S P digitalis assay method to determine the interrelationship of amotriphene and digitalis toxicity Studies were also conducted in 7 dogs and 7 monkeys administered amotriphene orally by stomach tube at doses of 10 0 to 25 0 mg /Kg for periods ranging from 3 days to 12 months Four dogs were titrated to death with continuous intravenous infusion of amotriphene

The in vitro cardiac activity of amotriphene was determined in isolated rabbit hearts by means of a modified Langendorf perfusion technique Inotropic changes were measured with a Grass FT 03 force displacement transducer Amotriphene was administered at log dose intervals of 25 to 200 micrograms per heart using 3 hearts and 3 injections of drug per heart for the determination of each point

Results

The response of intravenously administered amotriphene on heart rate blood pressure and heart contractile force in dogs is shown in Table I There was a decrease in heart rate systolic and diastolic blood pressure and an apparent moderate increase in heart contractile force The decrease in arterial pressure and the positive inotropic response were of relatively short duration (5 to 20 minutes) whereas the negative chronotropic response was considerably longer (20 to 90 minutes) There were no changes in the ECG at the lower doses Doses of 8 0 and 16 0 mg /Kg produced increasing changes in the ECG pattern consisting of an increase in the refractory period as measured by an increase in the corrected Q T interval and a slight increase in conduction time as measured by an increase in the QRS interval

The action of amotriphene on sinus tachycardia induced by penthienate bromide is shown in Table II Within the dosage range used there was a marked inhibition of the sinus tachycardia The duration of this negative chronotropic action ranged from 30 to 90 minutes

The results of the study of the action of amotriphene on digitalis toxicity are contained in Table III Of the total of 18 experimentally induced digitalis arrhythmias there were 12 complete reversions to normal sinus rhythm with amotriphene There were 5 partial reversions of which 3 resulted in partial heart block and there was 1 unsuccessful attempt at reversion The total dosage for reversion varied from 2 0 to 18 0 mg /Kg and the duration of complete reversion after the final administration of amotriphene ranged from 1 to 6 hours It should be recognized that this is a relatively short period of observation for this type of experiment and it is possible that had the experiments been followed for periods up to 12 hours there might have been some instances of reversion to a ventricular ectopic rhythm since it is anticipated that the duration of action of amotriphene is shorter than that of digitalis These experiments however do demonstrate the ability of amotriphene to bring about the conversion of a digitalis induced arrhythmia

The results of experiments conducted in cats using the U S P digitalis assay method are contained in Table IV Within the limits of these experiments amotriphene did not raise the lethal dose of digitalis Various other dosage schedules of amotriphene not contained in Table IV were also carried out but were unsuccessful In no instance were we able to significantly raise the lethal dose of digitalis We were

also unable to demonstrate any increased toxicity for the combination of amotriphene and digitalis within the limits of these experiments

The results of ECG studies in dogs and monkeys are summarized below Two dogs which received 10 mg /kg of amotriphene orally for 21 days developed no cardiac arrhythmias there was little change in heart rate and there were no changes in the refractory period or conduction time Five dogs which received 20 mg /kg of amotriphene for varying periods of medication up to 18 days had essentially the same ECG pattern as those which received 10 mg /kg There were no cardiac arrhyth mias changes in conduction time or refractory period Dogs which received the 20 mg dose did exhibit stimulation of the central nervous system In 2 animals this stimulation was sufficient to be fatal within 3 days after the start of drug therapy

The ECG pattern of activity for the 4 dogs titrated to death with amotriphene was similar for each animal This consisted of gradually increasing voltages in the S and T waves moderate changes in the P and R waves increased refractory period and conduction time and increased activity of the central nervous system which resulted in overt seizures and convulsions After the onset of marked stimulation of

Table I Cardiovascular changes induced by intravenous amotriphene in anesthetized dogs

Dose	Heart rate		Blood pressure		Heart contractile force
	Control ± S E (beats/min)	% Decrease	Control ± S E (mm Hg)	% Decrease in mean pressure	(% Increase ± S E)
mg /kg	177 4 ± 10 5	16 5	134 3 ± 6 7 / 100 7 ± 3 9	28 6	20 5 ± 4 5
4 mg /kg	136 0 ± 26 4	21 5	103 3 ± 21 4 / 73 3 ± 15 3	33 7	18 6 ± 5 1
8 mg /kg	96 0 ± 9 24	30 0	127 1 ± 8 5 / 73 6 ± 9 6	38 4	20 1 ± 6 8
16 mg /kg	151 5 ± 9 4	43 5	113 1 ± 9 9 / 80 0 ± 6 7	46 1	21 8 ± 8 3

Table II Action of amotriphene in anesthetized dogs with tachycardia induced by penthienate bromide

Dose	Heart rate		Blood pressure		Heart contractile force
	Control ± S E (beats/min)	% Decrease	Control ± S E (mm Hg)	% Decrease mean pressure	(% Increase ± S E)
1 mg /kg	228 0 ± 13 8	16 2	146 3 ± 16 5 / 112 ± 16 6	14 8	19 0 ± 5 6
2 mg /kg	193 7 ± 10 4	25 3	149 3 ± 7 1 / 113 6 ± 6 8	24 7	15 3 ± 6 1
4 mg /kg	272 0 ± 6 8	48 2	148 3 ± 1 2 / 99 2 ± 11 2	28 9	22 2 ± 7 9

Table III. Action of amotriphene on cardiac arrhythmias of digitalis toxicity in anesthetized dogs

Experiment number	Glycoside and dose (cat unit/Kg.)		Dose needed for reversion (multiples of 2 mg./Kg.)	Additional injections	Total dosage (mg./Kg.)	Time of final ECG (hours)
1	Ouabain	0.5	1	2	6.0	1.3
	Ouabain	0.5	2	1	6.0	1.0
3	Ouabain	0.5	3	0	6.0	1.2
4	Ouabain	1.0	Not reverted	7	14.0	1.0
5	Ouabain	0.5	2	2	8.0	1.5
6	Ouabain	0.5	1	0	2.0	2.0
7	Ouabain	0.5	5	0	10.0	3.8
8	Ouabain	0.5	2	0	4.0	2.0
9	Ouabain	0.75	2	2	8.0	3.0
10	Ouabain	0.5	5	4	18.0	2.5
11	Tincture	0.6	4 Incomplete to partial heart block	0	8.0	4.2
12	Tincture	0.75	2 Incomplete partial heart block	0	4.0	2.5
13	Tincture	1.2	3	1	8.0	4.5
14	Tincture	0.6	2	1	6.0	3.2
15	Tincture	0.75	1 Incomplete partial heart block	0	2.0	1.0
16	Digitoxin	0.83	2 Partial occasional runs of ectopic beats	0	4.0	2.5
17	Digitoxin	0.75	3 Partial occasional runs of ectopic beats	0	6.0	1.5
18	Digitoxin	0.50	1	0	2.0	6.0

Table IV. Comparison of digitalis assay in cats and amotriphene activity

Drug	Do (mg./Kg./5 min.)	Number of animals	Lethal dose (mg./Kg. ± S.E.)
Ouabain	0.005	5	0.115 ± 0.0019
Ouabain	0.0075	5	0.1095 ± 0.0038
Amotriphene	2.0	8	61.8 ± 7.0
Ouabain and amotriphene	0.0075 2.0	8	0.1012 ± 0.004

the central nervous system there were increasing periods of ventricular ectopic beats, heart block, runs of ventricular ectopic tachycardia, complete A-V dissociation, and eventually respiratory embarrassment coincident with a decerebrate rigidity and finally ventricular fibrillation. Final lethal doses of amotriphene ranged from 21 to 127 mg./Kg.

The 2 monkeys which received 12.5 mg./Kg. per day orally of amotriphene developed no cardiac arrhythmias, changes in refractory period, or conduction time. The only change observed was a slight increase in the voltage of the S and T waves.

The 5 monkeys treated with 25 mg./Kg. per day orally of amotriphene all exhibited the same pattern of ECG activity. This included moderate bradycardia, an increase in refractory period of 10 to 15 per cent, and an occasional increase in conduction time. Each animal developed moderate drug-induced arrhythmias of short duration. These were never consistent for the same animal. The arrhythmias developed approximately 2 hours after administration of the drug, and in almost all instances reverted to a normal sinus rhythm by 6 to 8 hours after administration of the drug. Changes consisted of partial heart block, occasional ventricular extrasystoles, and nodal rhythms. The T and S waves developed increased voltages, whereas the P and R waves remained unchanged.

The results of studies in isolated rabbit hearts demonstrated that amotriphene produced a small to moderate negative inotropic action on the myocardium. These results are shown in Table V. Earlier studies in intact dogs using the Walton strain gauge had shown amotriphene to have an apparent positive inotropic action. The 2 experiments conducted in sympathectomized dogs demonstrated that intrave

nously administered amotriphene produced a positive inotropic response before sympathetic block and a negative inotropic response after sympathetic block. It is probable therefore that the moderate positive inotropic response seen in the initial dog preparation was not due to direct cardiac stimulation of amotriphene but was probably due instead to reflex sympathetic cardiac stimulation initiated by the hypotension after administration of amotriphene.

Discussion

A unique combination of properties makes amotriphene an interesting therapeutic drug: it is a coronary dilator, has the ability to increase coronary sinus oxygen saturation,[4] is devoid of cardiac stimulating action, produces moderate bradycardia, and possesses antiarrhythmic properties.

Farah and Birnbaum[3] have reported amotriphene to be 4 and 8 times as effective as quinidine and Pronestyl, respectively, in increasing the refractory period of the isolated rabbit atrium and equal to quinidine in decreasing conduction velocity. They have also demonstrated the ability of amotriphene to produce a reduction in the auricular and ventricular rate of auricular flutter and fibrillation and to produce reversion to a normal sinus rhythm. The present studies have demonstrated the ability of amotriphene to revert the arrhythmias of digitalis toxicity to normal sinus rhythm. Thus there appears to be no contraindication for the concurrent use of digitalis and amotriphene. One may also surmise that amotriphene may play an important part in bringing about relief for the anginal patient who exhibits disturbances of rhythm since anginal pain has been reported by many investigators to be relieved after the abolishment of rhythm disturbances of many varieties and the re-establishment of a normal sinus rhythm.

The coronary dilator activity of amotriphene suggests that the drug may be effective in conditions of myocardial anoxia. Papaverine is moderately effective as a relaxant of smooth muscle and coronary dilator. Unfortunately, though it is effective in only a small percentage of clinical situations, and this may be due to the fact that it stimulates the myocardium to a proportionately greater extent than it increases coronary blood flow. Bobb and Green[[illegible]] have shown that amotriphene produces not only a greater mean coronary blood flow but also increases both the systolic and diastolic portions of coronary flow and at the same time causes no increase in myocardial contractility or change in the duration of systole. They have also demonstrated that amotriphene is similar in activity to but more potent than sodium nitrite.

Recently, Darby and Aldinger[[illegible]] have studied the cardiac pharmacology of nitroglycerin and have suggested that nitroglycerin may achieve its therapeutic efficacy through its ability to decrease the peripheral work load on the heart as well as its ability to increase coronary flow. In addition, and perhaps more importantly, they suggest that nitroglycerin may participate in the metabolism of the cardiac contractile mechanism in such a way as to increase its efficiency. Preliminary studies by this group indicate that amotriphene has a pattern of activity similar to that of nitroglycerin (personal communication from Darby). The moderate bradycardic action of amotriphene on the normal heart rate, the slight decrease it produces in blood pressure, and its slight negative inotropic action in the experimental animal all lend substance to the premise that this drug may reduce the peripheral work load of the compromised hypoxic heart. This property is in addition to its ability to dilate the coronary vascular bed and to increase coronary sinus oxygen saturation. In patients with marked sinus tachycardia, amotriphene would be expected to produce a greater degree of bradycardia than in the patient with a normal heart rate. In both

Table V. Amotriphene-induced changes in heart contractile force in the isolated rabbit heart

Dose (micrograms/heart)	% Decrease heart force
25	3.4
50	4.8
100	12.6
200	15.3

the epinephrine-driven heart[1] and the sinus tachycardia induced by a parasympatholytic drug as reported in this study amotriphene has demonstrated an ability to bring about a moderate to marked decrease in heart rate

The cardiovascular toxicity studies conducted in dogs and monkeys indicate that high doses of amotriphene are more neurotoxic for the dog than for the monkey In fact stilbenes in general to which amotriphene is related chemically are known to be particularly toxic to the dog as compared to man and other animals[9] However as with any drug that acts upon the conducting system of the heart to diminish automaticity amotriphene particularly in high doses may bring about disturbances in cardiac rhythm In man the level of drug needed to produce these effects probably exceeds by many fold the recommended therapeutic dosage level In those instances in which disturbances in rhythm do occur animal studies indicate that withdrawal of the drug brings about rapid reversal to a normal sinus rhythm

A recent report by Sandler[10] indicates that amotriphene was not significantly superior to a placebo in the relief of angina pectoris in 13 patients using a double blind technique Patients in this study were given amotriphene in a dose of 25 mg four times daily Recent unpublished clinical observations indicate that higher doses of amotriphene may be needed to produce significant relief in anginal like conditions The studies of Harris however indicate significant relief in anginal patients as indicated by increased work capacity and reduced requirements for nitroglycerin In addition Harris reported significant relief for patients with cardiac arrhythmias of both atrial and ventricular origin The experimental studies completed to date suggest an important pattern of activity that should be clinically useful

Summary

Amotriphene (Myordil WIN 5494) has been shown to have a coronary dilator activity about twice that of papaverine yet to be devoid of myocardial stimulant action Amotriphene will significantly reduce the sinus tachycardia induced by a parasympatholytic drug and will reduce to a lesser extent heart rates in normal animals Amotriphene is 4 and 8 times more active than quinidine and procaine amide respectively in increasing the refractory period of the isolated rabbit atrium It is equal to quinidine in decreasing conduction velocity It will reduce auricular and ventricular rate as well as produce normal sinus rhythm in experimentally induced auricular flutter and fibrillation Amotriphene will convert digitalis induced cardiac arrhythmias to a normal rate This combination of coronary dilator and cardiac antiarrhythmic properties of amotriphene is of potential value in the treatment of angina like conditions and the milder cardiac arrhythmias

REFERENCES

1 Karczmar A G Bourgault P and Elpern B Antiaccelerator coronary dilator and certain other pharmacologic actions of new polymethoxyphenyl derivatives Proc Soc Exper Biol & Med 98 114 1958
2 Bobb J R and Green H D Comparative effect of WIN 5494 on left coronary flow Fed Proc 17 17 1958
3 Farah A and Birnbaum L Decelerator and antiarrhythmic properties of amotriphene J Pharmacol & Exper Therap 127 128 1959
4 Page R G and Same L The effect of Myordil on coronary sinus oxygen saturation a possible explanation for the antiarrhythmic properties of this drug Clin Res 7 388 1959
5 Harris R Clinical observations on new coronary vasodilator (WIN 5494) Am J Cardiol 4 274 1959
6 Walton R P Leary J S and Jones H P Comparative increase in ventricular contractile force produced by several cardiac glycosides J Pharmacol & Exper Therap 98 346 1950
7 Brewster W R Jr Bunker J P and Beecher H K Metabolic effects of anesthesia VI Mechanism of metabolic acidosis and hyperglycemia during ether anesthesia in the dog Am J Physiol 171 37 1952
8 Darby T D and Aldinger E E Further studies of the effects of myocardial energy utilization elicited by nitroglycerin Circulation Res 8 100 1960
9 Cartler E G and Fidler H K Cerebral lesions produced in healthy dogs by the intravenous injection of 4 4 diamidino stilbene T Roy Soc Trop Med & Hyg 39 533 1946
10 Sandler G Clinical evaluation of new coronary vasodilator 3-dimethylamino-1 1 2 tris (4-methoxyphenyl) 1 propene hydrochloride (WIN 5494) Am Heart J 59 718 1960

Experimental study on the intramural distribution of the excitability cycle and on the form of the epicardial T wave in the dog heart in situ

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Although the spread of excitation through the ventricular wall has been studied extensively during recent years, little information is available about the spatial distribution of the repolarizing process. Because repolarization occurs much more slowly than depolarization, it cannot be investigated adequately with the available extracellular recording methods which are applied to the study of excitation. For technical reasons it has not yet been possible to investigate the electrical systole in its entire length in all layers of the ventricular wall by means of intracellular or suction electrodes. Therefore only indirect methods can be used for this purpose, of which determination of the excitability cycle has been applied already by Wilson and Herrmann in their studies on the ventricular gradient.

Recent studies by Hoffman and Cranefield[2] justify this approach, since they demonstrated that in normal conditions the time course of the threshold has a constant relation to the time course of the membrane action potential.

In some studies[3] the differences in the time of duration of the electrical systole in the endocardial and in the epicardial layers were determined. Such determinations do not necessarily indicate the temporal sequence of repolarization across the ventricular wall.

The technique which employs needle electrodes[4] makes possible the analysis of the excitability cycle at all levels within the ventricular wall.

The present study was undertaken in order to determine the temporal relations of the recovery process at different depths of the left ventricular wall and to correlate these findings with the polarity of the T wave in epicardial leads.

Methods

Eight mongrel dogs were used, anesthetized with a long-acting barbiturate. After intubation, respiration was maintained by a pump. The heart was exposed by a lateral thoracotomy and suspended in a pericardial cradle. Care was taken to prevent cooling and drying of the exposed heart by application of cotton wool soaked in warm saline and by closing the thorax thoroughly as soon as possible.

By means of a D.C.-operated heating blanket wrapped around the animal, the intrathoracic temperature was maintained at 37°C. The heart was driven at a constant rate by square wave pulses delivered by an independent stimulator to a bipolar electrode stitched onto the left auricle.

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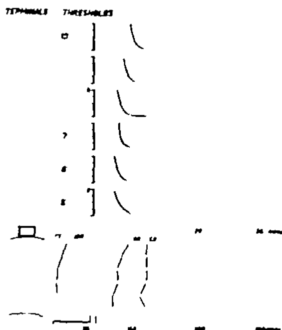


Fig. 1. Upper part: Strength/Interval curves for unipolar cathodal stimulation for all terminals of a needle electrode situated in the left ventricular wall of a dog's heart in situ. Thresholds determined at intervals of 5 msec. in the cardiac cycles. Horizontal: Intervals in the local excitability cycle. Vertical: Thresholds in multiples of the diastolic level. Dots indicate the end of the A.R.P., F.R.P. and T.R.P. Duration of testing pulses 0.5 msec. Lower part: Diagram of the temporal relations during activation and recovery of excitability. Horizontal: Intervals in the local excitability cycle. Vertical: Terminals of the needle electrode. Experiment of Sept. 6, 1956. Discussion in text.

Testing pulses were delivered to the terminals of a needle electrode[3] inserted into the mid anterolateral portion of the left ventricle. All intervals in the cardiac cycle were measured in respect to the time of occurrence of the intrinsic deflection in a unipolar lead from a terminal of a second needle electrode inserted as close as possible to the needle used for stimulation. For this purpose this lead was fed into a synchronizer starting the variable delay circuit of the testing stimulator. The excitability cycles of the different layers were analyzed by determining at every 5 millisecond interval the threshold for unipolar cathodal stimulation at each successive separate intramural terminal of the stimulating electrode. All stimuli were separated from earth without appreciable distortion by means of special 1:1 transformers. For recording and stimulating purposes, indifferent electrodes were placed subcutaneously on the extremities.

In some experiments cooling or heating of the epicardial surface was effected by applying without exerting appreciable pressure a pliable thin walled rubber tube on the epicardial surface around the head of the stimulating needle electrode. Through this tube water of 45° respectively 20°C. was circulated for a short time, while a new series of threshold determinations was carried out.

At every terminal the time of arrival of the excitatory wave was determined from the intrinsic deflection in unipolar leads and measured in regard to the intrinsic deflection in the reference lead. In addition the following measurements were made from the strength/interval curves obtained: (1) the end of the *absolute refractory period* (A.R.P.) as defined arbitrarily by the threshold reaching the 20 fold of the diastolic level[6]; (2) the end of the *functional refractory period* (F.R.P.) as defined by the threshold reaching the 1.5 fold of the diastolic level according to our findings described elsewhere[7]; (3) the end of the *total refractory period* (T.R.P.) as defined by the threshold reaching the diastolic level.

Results

A. Transmural sequence of recovery. The strength/interval curves for cathodal stimuli determined at the successive intramural terminals generally have the same contour (Figs. 1-3, *upper part*). Slight differences were caused by the temporal sequence of activation across the ventricular wall and by local variations in the duration of the refractory state.

The progress of recovery through the ventricular wall can be studied from the sequence of the end of different refractory periods. In our opinion the best available index of the restoration of excitability is the end of the F.R.P., since this marks the restoration of an essential property of myocardial tissue, the conduction of the excitatory wave.

Furthermore this point can be measured accurately from the strength/interval curves. In contrast, the end of the T.R.P. can only be estimated with an error of approximately 5-10 milliseconds because during this part of the cardiac cycle the thresh

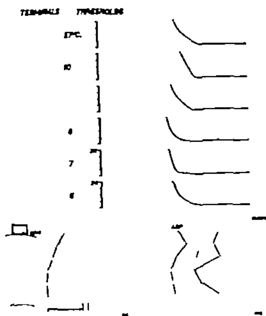


Fig 2 Same explanation as for Fig 1 Experiment of April 14 1956 Discussion in text

old declines rather gradually As can be seen from Figs 1 3 (*lower part*) the course of the end of the F R P in the successive intramural layers sometimes is rather erratic and does not follow the same sequence as that of the end of the A R P and F R P in these layers The end of the A R P as defined above can be determined without any appreciable error but its functional significance is dubious During heating and cooling of the epicardial surface however we sometimes had to resort to this accurately and quickly to determine mark point even if this introduces a slight error (Fig 4) The rapidity of the changes in the duration of the electrical systole prevented the determination of complete strength/interval curves for all terminals

In these experiments the functional recovery follows rather closely the same time course as the spread of activation through the middle and outer part of the ventricular wall In these layers the duration of the F R P is nearly equal In the innermost layer however the F R P sometimes is approximately 15 milliseconds longer than in the middle and subepicardial layers

These results show convincingly that recovery does not spread across the ventricular wall in a linear way and that predictions from determinations of the time course of excitability carried out at the endocardial and epicardial surfaces are erroneous The middle layers may show large deviations from such a linear spread because recovery may occur relatively early

B Heating and cooling of the epicardial surface In all control observations the the T wave was negative in unipolar leads from the epicardial surface near to the needle electrode In the experiment with a negative epicardial T wave illustrated in Fig 5 the end of the F R P in the layers just beneath the epicardial surface occurred approximately some 10 milliseconds earlier than in the subendocardial layers The negative epicardial T wave may be explained by a later repolarization in the middle and outer layers of the ventricular wall

During cooling of the epicardial surface the absolute refractory period is increased throughout the whole diameter of the

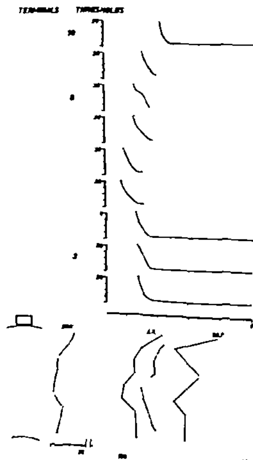


Fig 3 Same explanation as for Fig 1 Experiment of Feb 1 1956 Discussion in text

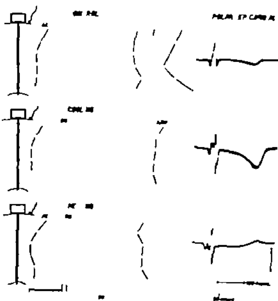


Fig 4 Temporal relations between activation and recovery of excitability for unipolar cathodal stimulation at all terminals of a needle electrode which are situated in the left ventricular wall of a dog heart in situ together with unipolar electrogram from epicardial terminal End of A R P F R P and T R P taken from complete strength/interval curves Duration of testing pulses is 0 5 msec Upper part Control Middle part During cooling epicardial surface Lower part During heating of epicardial surface Experiment of March 22 1956 Discussion in text

ventricular wall and a deep negative T wave is recorded from the epicardium The observed small differences in time of recovery between the individual layers do not predict such a large change in the voltage of the T wave

During heating of the epicardial surface a positive epicardial T wave is observed The A R P is now shortened throughout the ventricular wall The differences in time between the end of the refractory period in the different layers are rather small although consistent with the T wave changes according to the concept of the ventricular gradient

These observations led us to suppose that a change in the transmural sequence of restoration of the excitability was not the sole factor associated with the marked changes in the polarity of the epicardial T wave as has been postulated by Nahum and Hoff [8]

In some experiments the time relations in the restoration of excitability between this section of the ventricular wall and more distant parts of the ventricle were analyzed Fig 5 illustrates a typical experiment In this experiment, four needle electrodes were inserted into the anterolateral part of the left ventricular wall Three were placed respectively at the apex near to the coronary sulcus and close to the anterior septal part of the left ventricle Within the triangle formed by these three needle electrodes a fourth needle electrode was inserted (Fig 6 inset) the distance between it and the others was approximately 3-4 cm The head of this needle carried two electrodes in contact with the epicardial surface one of these was used for stimulation the other for recording

In the control observations at the epicardial terminal of the central electrode all refractory periods were completed later than in the corresponding layers at the other needle electrodes (Fig 6 upper part) The sequence of the completion of the A R P F R P and T R P in this part of the wall indicates that recovery occurred later in the outer parts of the wall This should lead one to expect a negative T deflection at the epicardial surface which indeed was observed

During heating of the epicardial surface the epicardial T wave became positive and the duration of all refractory periods was shortened (see Fig 5) The A R P of the outer layers is now shorter than in the inner layers and a positive T wave is expected The completion of the F R P occurs nearly synchronously in inner and outer layers but there is a large difference between the muscle layer in contact with terminal 11 at the epicardial surface and that near to terminal 10 The larger duration of the F R P at the latter terminal should lead one also to expect a positive T wave The sequence of the end of the T R P however is such that a negative T deflection from the epicardial surface should be expected

If one compares the duration of the refractory periods determined at the central terminal with those at the other terminals important differences in time are seen (Fig 6) During the control observations these differences indicate that repolarization occurs later at the central electrode and there a negative epicardial T wave is

observed Heating of the epicardial surface causes a diminution of all three refractory periods in the heated area which is now repolarized earlier than the surrounding parts The epicardial T wave is positive

Discussion

From these observations the conclusion can be drawn that the functional recovery of the myocardium follows a regular sequence across the ventricular wall Nowhere did we find evidence of an erratic progress of the end of the functional refractory period This indicates that an extrasystole arising after the end of the functional refractory period will be conducted in a homogeneous way and will meet no refractory tissue on its way when spreading in a direction perpendicular to the epicardial surface

It has been assumed that the sequence of repolarization across the ventricular wall can be deduced by interpolation of the determinations of the end of the electrical systole made on the endocardial and epicardial sides only

However it follows from our experiments that this assumption is not justified Large deviations may be present from a linear progress of recovery in the interposed muscle layers In the middle layers recovery may be more advanced than in the inner and outer layers This implies that the polarity of the epicardial T wave cannot be explained only on a basis of the difference in time of repolarization in inner and outer layers This view has been expressed before by Hoff and Nahum [9] We found it impossible in most cases to predict the polarity of the epicardial T wave from the temporal sequence of the completion of the A R P F R P and T R P through the different layers of the ventricular wall We feel that the method of determining the duration of the refractory periods across the ventricular wall does not give satisfactory information for this purpose

At least two other factors contribute to the polarity of the epicardial T wave Our findings demonstrate that also differences in time in the completion of recovery between the area near the recording electrode and the adjacent areas have to be considered

Furthermore we observed occasionally that at the beginning of heating of the

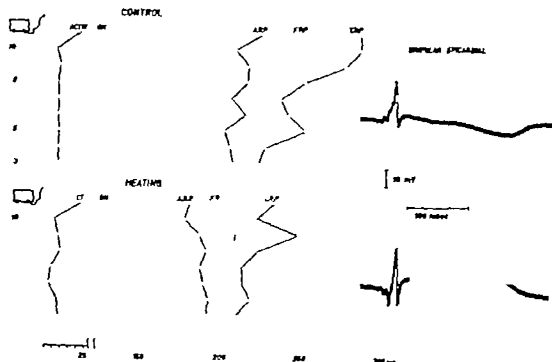


Fig 5 Same explanation as for Fig 4 *Upper part* Control *Lower part* During heating of the epicardial surface Experiment of Nov 2 1959 Needle electrode No 1 as indicated in Fig 6 inset Discussion in text

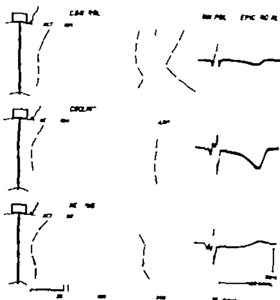


Fig 4 Temporal relations between activation and recovery of excitability for unipolar cathodal stimulation at all terminals of a needle electrode which are situated in the left ventricular wall of a dog heart in situ together with unipolar electrogram from epicardial terminal End of A.R.P F.R.P and T.R.P taken from complete strength/interval curves Duration of testing pulses is 0.5 msec Upper part Control Middle part During cooling epicardial surface Lower part During heating of epicardial surface Experiment of March 22 1956 Discussion in text.

ventricular wall and a deep negative T wave is recorded from the epicardium The observed small differences in time of recovery between the individual layers do not predict such a large change in the voltage of the T wave

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These observations led us to suppose that a change in the transmural sequence of restoration of the excitability was not the sole factor associated with the marked changes in the polarity of the epicardial T wave as has been postulated by Nahum and Hoff [8]

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During heating of the epicardial surface the epicardial T wave became positive and the duration of all refractory periods was shortened (see Fig 5) The A R P of the outer layers is now shorter than in the inner layers and a positive T wave is expected The completion of the F R P occurs nearly synchronously in inner and outer layers but there is a large difference between the muscle layer in contact with terminal 11 at the epicardial surface and that near to terminal 10 The larger duration of the F R P at the latter terminal should lead one also to expect a positive T wave The sequence of the end of the T R P however is such that a negative T deflection from the epicardial surface should be expected

If one compares the duration of the refractory periods determined at the central terminal with those at the other terminals important differences in time are seen (Fig 6) During the control observations these differences indicate that repolarization occurs later at the central electrode and there a negative epicardial T wave is

Case reports

Bacterial endocarditis associated with atrial septal defect of the ostium secundum type

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Bacterial endocarditis is a rare complication of atrial septal defect of the ostium secundum type. This observation is of particular interest since the defect is one of the most common congenital cardiac malformations seen at necropsy.[1] A review of the literature reveals only 4 cases of bacterial endocarditis associated with an isolated secundum atrial defect.[1]

The purpose of the present communication is to report an additional case of ostium secundum defect complicated by bacterial endocarditis. It was encountered in a study of 58 cases of bacterial endocarditis observed at the Babies Hospital in the past 30 years.

Case report

Clinical data. The patient was a 23-month-old white female infant with congenital cardiac malformation and urinary tract disease who was admitted to the hospital in 1959 because of fever.

PAST HISTORY. The infant was born at term and weighed 2.1 kilograms. A heart murmur was detected in the neonatal period. When the infant was 5 months of age, pyuria was noted in association with intermittent fever. There was marked retardation of growth and of psychomotor development.

At 8 months of age the infant was referred to the Babies Hospital for diagnostic evaluation. On examination at that time she was noted to be a small, poorly developed infant who perspired freely. She weighed 5.53 kilograms. There was no cyanosis or clubbing. A systolic thrill was palpable over the base of the precordium. Auscultation of the heart revealed a harsh systolic murmur which was maximal at the upper left sternal border; the pulmonic second sound was loud. The blood pressures obtained in an arm and a leg while the infant was crying were 104/[illegible]0 and 118/[illegible] mm. Hg, respectively. An electrocardiogram indicated normal sinus rhythm, rate of 130, P-R interval of 0.16 second, and right axis deviation. A chest roentgenogram showed cardiac enlargement. Congenital heart disease was diagnosed although the nature of the defect was not defined.

Urinalyses revealed intermittent pyuria and mild albuminuria; specific gravity varied between 1.006 and 1.026. Specimens of urine for culture which were obtained by catheterization were frequently sterile but occasionally yielded growth of bacteria. The organisms which were recovered either singly or in combination included *Staphylococcus albus hemolyticus*, *Staphylococcus aureus hemolyticus*, and *Streptococcus hemolyticus*. An intravenous pyelogram demonstrated bilateral hydronephrosis and hydroureter; the right ureter was convoluted. Although obstruction was not visualized in the genitourinary tract, it was suspected at the ureterovesical junctions.

The patient remained in the hospital for 4 months and failed to show any gain in weight. Neurological evaluation suggested the diagnosis of congenital cerebral defect with spastic paraplegia and mental retardation. She had a few mild elevations of temperature for 1 to 2 days; the cause of the fever was usually obscure. The patient received no specific therapy and was discharged at 12 months of age.

PRESENT ILLNESS. Twelve days prior to readmission to the Babies Hospital the infant became very irritable and was noted to have a fever of 103°F. Subsequent daily elevations of temperature occurred and reached a maximum of 106.5 F. She had anorexia and was lethargic.

PHYSICAL EXAMINATION. The vital signs recorded on admission were: temperature 10[illegible]4 F, pulse 140, and respirations 24. Systolic blood pressure

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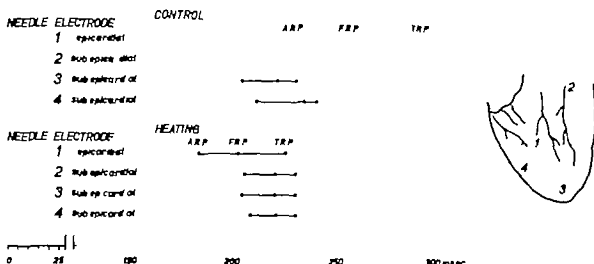


Fig 6 Same experiment as Fig 5 Temporal relations in recovery of excitability for unipolar cathodal stimulation of outermost terminals of 4 needle electrodes the left ventricular wall of a dog heart in situ Duration of testing pulses is 0 5 m ec *Upper part* Control *Lower part* During heating of epicardial surface around needle electrode *Inset* Position of needle electrodes Discussion in text

epicardial surface a positivity of the T wave could be replaced in a few seconds by a negativity by lifting the heating tube from the epicardial surface positivity re appeared immediately when the heating ibe was replaced on the epicardial surface This means that in these cases the sequence of repolarization in the outermost layer was the nly determining factor to the polarity of the epicardial T wave

Summary

By means of needle electrodes the time course of excitability was studied at dif ferent depths of the left ventricular wall of intact dog hearts The results indicate that the end of the functional refractory period progresses through the wall in an endocardial epicardial direction and follows rather closely the pattern of activation This progression does not follow a linear course indicated by the end of the re fractory period at the endocardial and epicardial surfaces n most cases recovery of excitability was more advanced in the middle layers than in the subendocardial and outer wall Experiments in which the epicardial surface was heated or cooled indicate that the polarity of the T wave cannot be predicted from the general direc tion of recovery across the ventricular wall but is also influenced by temporal dif ferences in the completion of recovery between adjacent parts

REFERENCES

1 Wilson F N nd Herrmann G P A xperimental study of ncomplete bundle branch block and of the refractory period of the heart of the dog Heart 8 229 1921
2 Hoffman B F and Cranefield P Electro physiology of the heart New York 1960 McGraw Hill Book Co Inc
3 Reynolds E W nd Vander Ark C R An experimental study on the origin of T w es based on determinations of effectiv refractory period from epicardial and endocardial aspects of the entricle Circulation Res 7 943 1959
4 Pipberger H Schwartz L Massumi R A and Prinzmetal M Studies on the nature of the repolarization process Ann New York Acad Sc 65 974 1957
5 Durrer D and Van der T eel L H Excita tion of the left entricular wall of the dog and goat Ann New York Acad Sc 65 779 1957
6 V Dam R Th Durrer D Van der Tweel L H nd Strackee J The excitability cycle of the dog left ventricle determined by anodal cathodal and bipolar stimulation Circulation Res 4 196 1956
7 Durrer D Van Dam R Th and Van der T eel L H Origin and propagation of extra systoles resulting from stimulation during d astole and during the refractory period of the dog heart Acta physiol et pharmacol neerl (I press)
8 Nahum L H and Hoff H E The nature of the precordial electrocardiogram Am J Phy iol 155 15 1948
9 Hoff H E and Nah m L H Comparison of the electrographic changes produced by heating and cooling epicardial and endocardial surfaces of the dog entricle Am J Physiol 153 176 1948

Microscopic examination (1) *Mycotic aneurysm*—The outer wall was composed of vascular connective tissue infiltrated with lymphocytes polymorphonuclear leukocytes and a few eosinophils The central core was composed of vegetations consisting of granular eosinophilic material bacteria and leukocytes The adjacent myocardium was edematous and showed loss of striations The endocardium was replaced by a layer of degenerating muscle fibers with bacteria on the surface (2) *Vegetation on the pulmonic valve*—This was composed of granular eosinophilic material in which were large clumps of bacteria and fragmented leukocytes The surface of the vegetation appeared fibrinous (3) *Plaques on the cusps of the pulmonic valve*—These consisted of bacteria superimposed on small areas of endothelial proliferation Gram positive cocci in pairs short chains and dense clumps were found in the sections through the mycotic aneurysm the pulmonic vegetation and plaques

LUNGS Grossinfarcts were present in the upper and lower lobes of the right and left lungs Friable thrombi were seen in the branches of the pulmonary artery leading to the areas of infarction Clumps of Gram positive bacteria were observed in some sections of the thrombotic material

GENITOURINARY TRACT The right kidney weighed 50 grams and the left 26 grams The cut surface of the right kidney showed the architecture to be well preserved whereas that of the left kidney was destroyed The left renal pelvis and calyces were more markedly dilated than those on the right Fine yellow gravel was present in the pelvis of each kidney There were four large calculi in the right ureter The ureters were tortuous dilated and had hypertrophied walls Both ureterovesical junctions were patent but narrow The bladder was dilated and hypertrophied there was no obstruction or abnormality of the urethra

Microscopic examination showed interstitial pyelonephritis of the left kidney In the right kidney numerous glomeruli contained capillary emboli Chemical analyses of the ureteral calculi indicated calcium phosphate and large amounts of carbonate

Anatomic diagnosis (1) Bacterial endocarditis of the pulmonic valve with mycotic aneurysm of the wall of the outflow tract of the right ventricle (2) Congenital malformation of the heart atrial septal defect of the ostium secundum type (3) Infarcts of the right and left lungs (4) Renal calculi bilateral and ureteral calculi right Hydronephrosis and hydroureter bilateral Interstitial pyelonephritis left Focal embolic glomerulonephritis right Hypertrophy and dilatation of the bladder (neurogenic?)

Discussion

The source of the bacteremia in this case was probably infection of the abnormal genitourinary tract This is suggested by the history of intermittent pyuria since early infancy the urographic evidence of bilateral hydronephrosis at 8 months of age and the necropsy findings of renal and ureteral calculi formation and pyelonephritis The organism which was recovered from blood culture *Streptococcus hemolyticus* may have been a member of the enterococcus group of streptococci These organisms have frequently been incriminated in patients with genitourinary tract infection and endocarditis

The localization of the bacterial endocarditis on the pulmonic valve was most likely determined by the underlying congenital cardiac malformation namely atrial septal defect of the ostium secundum type In cases of right sided bacterial endocarditis without pre existing heart disease the tricuspid valve is the most common site of infection[3] The presence of a cardiac malformation predisposes specific endocardial sites to hemodynamic injury which favors the implantation of microorganisms during bacteremia Traumatic endocardial lesions resulting from the development of pressure gradients across a defect or a deformed valve have been described in those cardiac anomalies commonly associated with bacterial endocarditis e g ventricular septal defect pulmonic stenosis patent ductus arteriosus etc In large secundum atrial defect however left to right shunting of blood occurs through the defect without a significant pressure gradient Endothelial jet lesions have not been described on the rim of the defect or in the atria and patients with isolated secundum atrial defect are not prone to the development of bacterial endocarditis

There is evidence to suggest hemodynamic trauma to the pulmonic and tricuspid valves in ostium secundum atrial defect which would theoretically increase the susceptibility to infection in these areas The augmented blood flow from the intracardiac shunt may produce turbulence across the valves of the right heart Intracardiac phonocardiography in patients with secundum atrial defect has provided indirect evidence of increased flow and vortex formation around these valves murmurs which have been recorded in the right ventricle during diastole and in the pulmonary artery during systole are attributed to functional stenosis of the tricuspid and pulmonic valves respectively[11] Furthermore observations from cardiac catheterization of patients with secundum atrial defect and large left to right shunts have

frequently documented pressure gradients across the pulmonic valve.[13] The disappearance of the gradient after surgical closure of the defect has verified the impression of relative pulmonic valvular stenosis due to increased flow. Since there have not been histologic observations of endocardial injury to the pulmonic and tricuspid valves in secundum atrial defect, one may infer that marked increase in pressure is a more important factor than flow in the production of hemodynamic lesions.

It is interesting to note in the necropsy findings of this case that there was endothelial proliferation underneath the small plaques of bacteria on two cusps of the pulmonic valve. These focal areas of fibrous reaction were probably a response to bacterial invasion, but they may also have been due to pre-existing hemodynamic trauma. The massive vegetation on the pulmonic valve was the source of multiple pulmonary emboli and infarcts. The mycotic aneurysm in the wall of the right ventricular outflow tract was probably caused by direct bacterial invasion from the pulmonic valve. The only evidence of systemic arterial embolization was mild focal embolic glomerulonephritis. The formation of peripheral emboli in cases of right-sided endocarditis in which there is no intracardiac right to left shunt may be related to pulmonary venous thrombosis secondary to pulmonary infarction.[14]

The observations at postmortem examination in the present case are almost identical to those in the first case of bacterial endocarditis associated with an atrial septal defect described by Griffith[3] in 1906. He reported the necropsy of a 15-year-old girl with an ostium secundum defect which measured "one by one and a half inches" and endocarditis predominantly of the pulmonic valve. A huge fungating mass of vegetations which was attached to the valve communicated with a mycotic aneurysm at the base of the pulmonary artery and right ventricular outflow tract. It is of particular interest that the tricuspid valve was also involved; one small fibrinous vegetation was adherent to the commissure between the septal and anterior leaflets. The mitral valve was normal and free of inflammatory lesions.

In the other three cases of bacterial endocarditis with secundum atrial defect reported in the literature the localization of the vegetations was as follows: on the limbus of the fossa ovalis and mitral valve in one, on the left atrial wall in one, and not described in the third case except for a statement that the rim of the defect was not involved.[4-6] In none of these reports was there a complete anatomic description of the heart; in only one of them were the size and position of the atrial defect and the appearance of the mitral valve noted.[7] These reports did not include either a bacteriologic diagnosis or a histologic description of the endocardial lesions. In the absence of this information the existence of bacterial endocarditis with an isolated ostium secundum defect in these cases is incompletely established.

The presence of deformities of the mitral or tricuspid valves may increase the susceptibility of patients with atrial septal defect to the development of bacterial endocarditis. Two cases of ostium secundum defect and mitral stenosis, the so-called Lutembacher syndrome, have been reported[15,16] in which bacterial vegetation occurred on the mitral valve. In ostium primum or low atrial defect (partial form of common atrioventricular canal), malformations of the mitral and/or tricuspid leaflets invariably occur which may produce valvular insufficiency. Bacterial endocarditis in one case of ostium primum defect has been well documented;[17] the vegetations were implanted on the atrial surface of the cleft aortic leaflet of the mitral valve and extended onto the adjacent septal leaflet of the tricuspid valve. In her review of the incidence of bacterial endocarditis, Abbott[3] has tabulated 57 cases of atrial septal defect; among 44 with "defects of the upper portion (ostium secundum)" bacterial endocarditis was not present, whereas 6 of 13 with "defects of the lower portion" had this complication. The location of the vegetations in the cases with low atrial defect, presumably ostium primum, was not described.

Summary

The clinical and necropsy findings in a 23-month-old infant with an atrial septal defect of the ostium secundum type com

plicated by bacterial endocarditis are presented. A massive vegetation was located on the pulmonic valve and communicated with a mycotic aneurysm in the wall of the right ventricular outflow tract. These lesions were almost identical to those described in the first reported case of endocarditis with ostium secundum defect. Three other cases recorded in the literature are reviewed.

Patients with large secundum atrial defect are not prone to the development of bacterial endocarditis although there is evidence for hemodynamic turbulence and possible trauma to the valves of the right heart. It is suggested that additional deformities of the mitral and tricuspid valves may increase the susceptibility of patients with atrial septal defect to bacterial endocarditis.

The author wishes to express sincere appreciation to Dr. Dorothy H. Andersen for her interest and valuable help in reviewing the necropsy material of this case.

REFERENCES

1. Gelfman, R., and Levine, S. A.: The incidence of acute and subacute bacterial endocarditis in congenital heart disease, Am. J. M. Sc. 204:324, 1942.
2. Abbott, M.: Incidence of bacterial inflammatory processes in cardiovascular defects and on malformed semilunar cusps, Ann. Clin. Med. 4:189, 1925.
3. Gould, S. E.: Pathology of the heart, ed. 2, Springfield, Ill., 1960, Charles C Thomas, Publisher.
4. Roesler, H.: Interatrial septal defect, Arch. Int. Med. 54:339, 1934.
5. Griffith, T. W.: A case of infective endocarditis involving the pulmonary valves and associated with imperfection of the interauricular septum, Lancet 2:973, 1906.
6. Jacobius, H. L., and Moore, R. A.: Incidence of congenital cardiac anomalies in the autopsies at New York Hospital, J. Tech. Method 18:133, 1938.
7. Bedford, D. E., Papp, C., and Parkinson, J.: Atrial septal defect, Brit. Heart J. 3:37, 1941.
8. Cosby, R. S., and Griffith, G. C.: Interatrial septal defect, Am. Heart J. 38:80, 1949.
9. Blumenthal, S., Griffith, S. P., and Morgan, B. C.: Bacterial endocarditis in children with heart disease, Pediatrics 26:993, 1960.
10. Hunter, T. H., and Paterson, P. Y.: Bacterial Endocarditis, DM — Disease-a-Month, Chicago, 1956, Year Book Publishers, Inc.
11. Edwards, J. E., and Burchell, H. B.: Endocardial and intimal lesions (jet impact) as possible sites of origin of murmurs, Circulation 18:946, 1958.
12. Lewis, D. H., Ertugrul, A., Deitz, C. W., Wallace, J. D., Brown, J. R., Jr., and Moghadam, A.: Intracardiac phonocardiography in the diagnosis of congenital heart disease, Pediatrics 23:837, 1959.
13. Blount, S. G., Jr., Swan, H., Gensini, G., and McCord, M. C.: Atrial septal defect. Clinical and physiologic response to complete closure in 5 patients, Circulation 9:801, 1954.
14. Bain, R. C., Edwards, J. E., Scheifley, C. H., and Geraci, J. E.: Right-sided bacterial endocarditis and endarteritis, Am. J. Med. 24:98, 1958.
15. Geiger, A. J., and Anderson, H. C.: Lutembacher syndrome complicated by acute bacterial endocarditis; report of a case diagnosed during life, Am. Heart J. 33:740, 1947.
16. Kurz, E. R. H., and Fischer, I.: Lutembacher syndrome associated with subacute bacterial endocarditis, New England J. Med. 240:178, 1949.
17. Rogers, H. M., and Edwards, J. E.: Incomplete division of the atrioventricular canal with patent interatrial foramen primum, Am. Heart J. 36:28, 1948.

Mechanisms influencing conduction in a case of intermittent bundle branch block

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The purpose of this report is to present a case of intermittent left bundle branch block in which the effects of a variety of physiologic maneuvers and pharmacologic agents were tested in an attempt to find trigger mechanisms which alter intraventricular conduction.

Previous authors writing about the phenomenon of intermittent left bundle branch block frequently raised the question of the mechanisms favoring normal and abnormal intraventricular conduction. Vessel[1] suggested that when a *critical heart rate* was exceeded conduction through the diseased bundle became impaired and left bundle branch block was produced. In support of this theory several authors[2-4] have presented case reports which showed that a small increase in heart rate was followed by a change from normal to aberrant intraventricular conduction. Other cases have been reported in which the alteration from normal to abnormal conduction was unattended by any change in heart rate. Finally, bundle branch block has been observed to develop during slowing of the heart rate.[5]

The present case afforded an opportunity for studying some of the variables involved in intermittent bundle branch block.

Case report

Present illness. This was the first admission to the Durham Veterans Administration Hospital for this 46-year-old white man. His chief complaint was chest pain on exertion. The patient had a documented anterior wall myocardial infarction which had occurred 14 months prior to admission. He gave no history of previous angina pectoris. Subsequent to the myocardial infarction the patient had been unable to work because of recurrent oppressive substernal chest pain on exertion or with excitement. He also gave a history of mild shortness of breath on exertion but denied orthopnea, nocturnal dyspnea, or edema. Four years prior to admission the patient was found to have mild hypertension. One year prior to admission the patient was told that his electrocardiogram showed some form of heart block.

Physical examination. The blood pressure was 130/80 mm. Hg, pulse 92, and respirations 12. The patient was a well-developed, slightly obese white man. Examination of the eye grounds showed Grade I hypertensive retinopathy. Examination of the chest revealed a few moist râles at the base of the left lung. The heart was enlarged to the left. The heart sounds were normal with a prominent atrial gallop and a faint ventricular gallop. Upon examination of the abdomen the edge of the liver was palpable two fingerbreadths below the right costal border. The remainder of the physical examination was within normal limits.

Laboratory clinical findings. Hemoglobin was 16.2 Gm. per cent with normal white blood cell count and differential. Urinalysis was normal. Stool guaiac was negative. The chest x-ray examination showed cardiomegaly with a cardiothoracic ratio of 15.2/28.2. Chemistries were reported as follows: fasting

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blood sugar 106, blood urea nitrogen 20, cholesterol 239, total protein 6.9 with a normal A/G ratio. Gall bladder series was reported to be normal. Phenolsulfonphthalein test was 75 per cent in 2 hours. The initial electrocardiogram was interpreted as showing left bundle branch block. A second electrocardiogram recorded 2 days later showed normal intraventricular conduction with prominent Q wave in Lead aV and absent R waves in the right precordial leads.

Methods

The physiologic maneuvers studied were performed under constant electrocardiographic monitoring. Control tracings were made with the patient lying quietly on an examining table. Exercise was studied by having the patient leg pedal with maximum effort while in the supine position or on occasion do rapid deep knee bends in the standing position. Valsalva and Muller maneuvers were performed in the usual way and were held for a period of 20 to 30 seconds. When arterial occlusive cuffs were used they were placed around all four extremities and released after a 5 minute period. Alterations in blood gas were induced by having the subject inhale 10 per cent oxygen or 10 per cent carbon dioxide for 3 to 5 minutes. Carotid sinus pressure was applied to the right side for varying periods of time and with varying force. Ocular pressure was applied over both eyeballs simultaneously. Between studies there was a period of rest and equilibration.

Pharmacologic agents were administered to the subject under electrocardiographic monitoring. The drugs, dosages, modes of administration, and results of each are listed in Table II. All of the agents were administered intravenously except for Methacholyl and amyl nitrite which were given subcutaneously and by inhalation respectively.

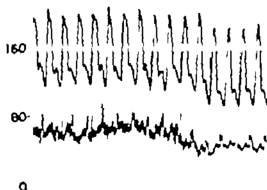


Fig. 1. Exercise.

Blood pressures were determined with the standard cuff and on occasion were measured directly from an intra-arterial needle with the use of a Statham strain gauge and a photographic recorder.

Results

Results of the various physiologic maneuvers are summarized in Table I. Exercise served as a consistent method of producing aberrant conduction (Fig. 1). At least 15 seconds of exercise by the patient in the supine position were required before conversion of normal conduction to bundle branch block. During this time there was an increase in heart rate of 40 to 60 beats per minute and a rise of blood pressure from control levels of 140/90 to 200/120 mm. Hg. With the patient in the upright

Table I. Physiologic maneuvers performed

Maneuver	Control period		Response	
	Rate	Conduction	Rate	Conduction
Exercise supine	80–115	Normal	120–140	Left bundle branch block
Exercise standing	90–115	Normal	117–140	Left bundle branch block
Arterial cuff release	90–170	Normal	125–130	Left bundle branch block
Valsalva maneuver	100–110	Normal	120–130	Normal
Muller maneuver	90–110	Normal	0–100	Normal
Oxygen—10 per cent	100	Normal	140	Normal
Carbon dioxide—10 per cent	108	Normal	135	Normal
Carotid sinus pressure	94–1 2	Left bundle branch block	72–98	Normal
Carotid sinus pressure	80–100	Normal	45–60	Left bundle branch block
Ocular pressure	100–120	Left bundle branch block	105	Left bundle branch block

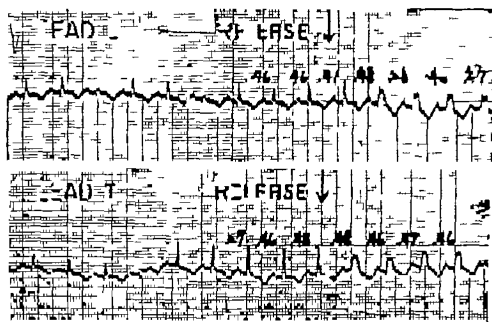


Fig. 2. Valsalva maneuver.

position aberrant conduction followed one to ten deep knee bends. When conversion occurred after only one knee bend the heart rate had increased by only two beats per minute. On other occasions as many as ten knee bends were performed prior to conversion and there was an associated increase in heart rate of 20 to 50 beats per minute.

The release of arterial occlusive cuffs when the patient was in the standing position resulted in conversion to bundle branch block within 10 seconds; this was associated with an increase in heart rate of 10 to 25 beats per minute.

The Valsalva maneuver produced an increase in heart rate of 10 to 30 beats per minute with maintenance of normal intraventricular conduction. Upon *release* of the Valsalva maneuver normal conduction converted to bundle branch block within one to three beats on several occasions (Fig. 2). Aberrant conduction did not occur on release of the Valsalva maneuver while arterial pressures were being recorded. However, it can be seen from Fig. 3 that mean and diastolic blood pressures reached very low levels during the period immediately after release of the Valsalva maneuver. The Müller maneuver had only a slight effect on heart rate and did not alter intraventricular conduction.

Inhalation of 10 per cent oxygen or 10 per cent carbon dioxide led to a tachycardia of 130 to 140 beats per minute without any change in intraventricular conduction. It was also noted that the breathing of 100 per cent oxygen did not prevent the consistent conversion to bundle branch block after exercise.

The various responses to carotid sinus pressure are illustrated in Fig. 4. The arrows indicate the points at which carotid sinus pressure was applied. *Tracing A* demonstrates the ease with which bundle branch block could be converted to normal intraventricular conduction with light carotid sinus pressure. Tracings *B*, *C*, and *D* illustrate the responses to more forceful carotid sinus pressure. In each case it can

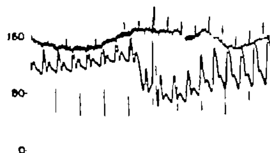


Fig. 3. Valsalva release.

be seen that aberrant conduction followed a period of prolonged asystole and was then followed by conversion to normal intraventricular conduction Tracing *F* illustrates that atropine blocked the effects of carotid sinus pressure on bundle branch block induced by exercise Tracing *G* shows that bundle branch block beats persisted during prolonged carotid sinus pressure in spite of marked bradycardia The finding of aberrant beats during vagal induced bradycardia led us to examine the effect of carotid sinus pressure on normal conduction Tracing *D* illustrates such a study and demonstrates that carotid sinus pressure can induce bundle branch block In Fig 5 it is shown that the conversion to bundle branch block during carotid sinus pressure is associated with a prolonged period of asystole and is attended by a marked fall in mean arterial blood pressure

The results of the studies in which pharmacologic agents were given are presented in Table II Potassium and Pronestyl each resulted in conversion of normal conduction to bundle branch block On separate occasions conversion occurred during an increase decrease or no change in heart rate Calcium or molar sodium lactate rapidly converted bundle branch block induced by potassium or Pronestyl to normal intraventricular conduction

Inhalation of amyl nitrite when the patient was in the standing position resulted in a change from normal to aberrant conduction with an associated increase in heart rate of only two beats per minute Inhalation when he was in the supine position had no effect on intraventricular conduction

Atropine produced a tachycardia of 122 beats per minute without any change in intraventricular conduction

The administration of Isuprel resulted in an increase in heart rate from a control level of 88 beats per minute to 170 beats per minute There was no change from normal intraventricular conduction throughout the period of infusion Transiently during this study the P R interval shortened from a control of 0 20 to 0 08 second We have observed similar shortening of the P R interval in normal subjects during infusion of Isuprel over and above the shortening associated with increased heart rate

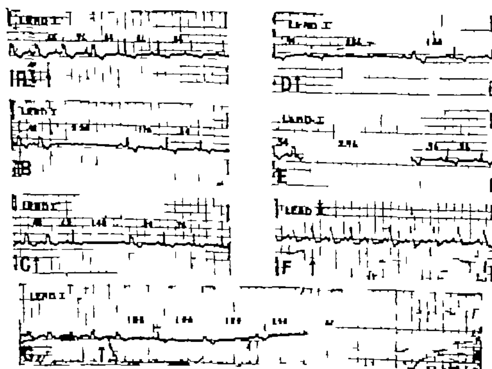


Fig 4 Varying responses to carotid sinus pre



Fig 5 Carotid sinus pressure

Tensilon Mecholyl and aminophylline had only slight effects on cardiac rate and did not lead to any alteration in intraventricular conduction

Discussion

The case reported illustrates the phenomenon of intermittent left bundle branch block Unstable bundle branch block of this type was first described by Lewis[6] in 1913 This is not a rare conduction abnormality as Comeau Hamilton and White[7] noted in 1938 They also pointed out that most cases of intermittent left bundle branch block occurred in a setting of organic heart disease The etiology of the conduction disturbance in this case was presumed to be coronary artery disease based on a history of angina pectoris and a documented myocardial infarction

Mechanisms favoring normal and abnormal conduction in cases of intermittent left bundle branch block have been discussed by many clinical investigators over a 30 year period Vesell[8] reported two cases which clearly demonstrated that this type of intraventricular conduction may be very susceptible to changes in cardiac rate Eichert[9] showed that whereas rapid heart rates favored conversion to bundle branch block and slow heart rates favored normal conduction there was considerable overlap between the two forms of conduction with respect to rate

Exercise served as a consistent way of inducing left bundle branch block in our patient It was our initial impression that conversion to left bundle branch block with exercise was related to the associated increase in heart rate We attempted to evaluate this hypothesis by inducing tachycardia comparable to that produced by exercise using atropine Isuprel or inhalation of carbon dioxide Tachycardia induced by these agents failed to produce bundle branch block

Termination of bundle branch block by carotid sinus pressure has been reported previously and has been attributed to slowing of the heart rate below a critical level[1, 11] In our patient carotid sinus pressure served as a consistent method of converting bundle branch block to normal intraventricular conduction However we noted that during *forceful* carotid sinus pressure blocked conduction persisted for several beats despite marked bradycardia To our surprise we also noted that forceful carotid sinus pressure consistently induced conversion from normal intraventricular conduction to bundle branch block This case appears to be unique by being the first

Table II Pharmacologic agents administered

Agent	*Dose*	*Control period*		*Response*	
		Rate	*Conduction*	*Rate*	*Conduction*
Pronestyl	200 mg I V	110 118	Normal	95 100	Left bundle branch block
Potassium	40 mEq I V	94 100	Normal	97 108	Left bundle branch block
Calcium gluconate	1 0 Gm I V	100	Left bundle branch block	85	Normal
Molar sodium lactate	100 mEq I V	107	Left bundle branch block	84	Normal
Amyl nitrite	Inhalation	120	Normal	122	Left bundle branch block
Atropine	2 0 mg I V	100	Normal	122	Normal
Isuprel	004 mg /min I V	88	Normal	170	Normal
Aminophylline	500 mg I V	102	Normal	118	Normal
Mecholyl	20 mg subcutaneously	110	Normal	116	Normal
Tensilon	1 0 mg I V	100	Left bundle branch block	84	Left bundle branch block

in which carotid sinus pressure both terminated and induced bundle branch block in the same patient

The observations made on the patient during exercise pharmacologically induced tachycardia and carotid sinus pressure illustrate that both bundle branch block and normal intraventricular conduction may occur at slow and rapid heart rates Normal conduction was recorded at heart rates from 38 to 172 bundle branch block was recorded at heart rates from 45 to 160 It is our opinion that this wide overlap (Fig 6) eliminates heart rate per se as the primary determinant of the type of intraventricular conduction in this patient

It was our impression that the type of intraventricular conduction during carotid sinus pressure was related to the force applied to the sinus In an attempt to evaluate this hypothesis we sought to establish what relationship if any existed between the degree of prolongation of the R R interval and the form of the ventricular complex This relationship is illustrated in Fig 7 When during carotid sinus pressure the R R interval was less than 1 2 seconds the

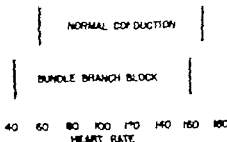


Fig 6 Heart rates with normal conduction and bundle branch block

ventricular complex was normal When the R R interval was greater than 1 4 seconds the form of the ventricular complex was that of left bundle branch block This relationship held regardless of the type of intraventricular conduction prior to carotid sinus stimulation It is tempting to postulate from this data that increased vagal tone can itself induce bundle branch block, but it will be seen from subsequent discussion that alternative mechanisms may be operative and that a cause and effect relationship has not been demonstrated

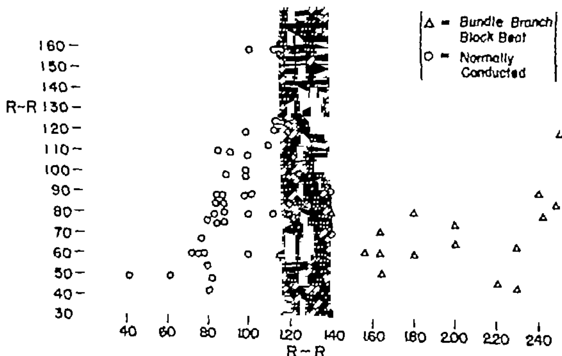


Fig 7 The relationship of the ventricular complex form to the R R interval during carotid sinus pressure Plotted on the abscissa are the R R intervals between each beat recorded during carotid sinus pressure For purpose of spread only the R R intervals preceding that recorded on the abscissa are plotted on the ordinate

Review

Alcoholic cardiomyopathy

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It is now custom to apply the term *cardiomyopathy* to any affection including hypertrophy of the myocardium which is not part of such common states as hypertension or coronary arterial valvular and congenital heart disease Only within recent times has it become known that alcohol is a frequent cause

The delay in such recognition is explained by a set of circumstances which include the stealthy development of the condition the sparsity of physical signs in its early stages a misinterpretation of the cause of an arrhythmia which it commonly exhibits the erroneous assumption that the harmful effects of alcoholism make themselves known as a beriberi syndrome the wrongful conclusion that certain electrocardiographic changes and later on heart enlargement with heart failure have been the outcome of coronary arterial disease and the inattention paid to insular changes in a hypertrophied myocardium at necropsy

Because alcoholic cardiomyopathy in its early stages can be halted its prompt diagnosis is rewarding for abstinence from spirit-drinking before it has exerted serious and irretrievable damage on the heart muscle will enable a patient to regain his customary health A familiarity with its clinical and electrocardiographic presentation therefore assumes exceptional importance

Clinical features

The chief characteristic which marks the progress of the injurious effects of alcohol on the heart is the insidious way in which they creep in Thus many months or even years may pass before the undisguised spectacle of cardiac involvement is laid bare

Palpitation may be the first symptom to appear in alcoholic cardiomyopathy taking the form either of paroxysmal tachycardia or more often of auricular fibrillation Indeed fibrillation in the absence of its more common causes such as mitral stenosis thyroid toxemia cardiac infarction hypertension and constrictive pericarditis is likely to be the outcome of excessive spirit drinking and in this circumstance it is for the clinician to extract this confession through persistent interrogation of the patient or his relatives if necessary

Of great significance too is the finding in an adult of extrasystoles in company with a moderate tachycardia of 90 or so per minute It should be recalled that extrasystoles do not like tachycardia so that if these two states are found side by side cardiomyopathy from alcoholism is the usual explanation

Bundle branch block either in sinus rhythm or associated with fibrillation is a common conduction defect and complete heart block is not rare

Moderate *breathlessness* is also a common initial symptom In that the complaint is not an arresting one during the early phase of the illness it is not infrequently attributed to obesity which is almost invariably present

Chest pain is not a symptom of alcoholic

From the Cardiac Department London Hospital London E England
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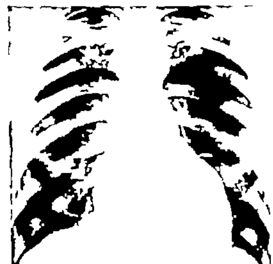


Fig 1 Moderate enlargement of the heart with early pulmonary congestion

cardiomyopathy but should it be a fortuitous finding it gains importance when the subsequent electrocardiogram shows changes which may lead erroneously to the assumption that cardiac infarction is providing a source for the pain

At a *later stage* of the illness breathlessness increases and becomes a distressing symptom for it is then accompanied by the more sinister signs of heart failure which include a prominent venous pulse which frequently shows a diastolic dip greater cardiac enlargement triple heart rhythm a pansystolic murmur from dilatation of the mitral or tricuspid rings initiating mitral or tricuspid regurgitation crepitations at the lung bases over which fluid collects and even edema of the ankles

Radiology During the early phase of the illness the heart when viewed radiologically may appear natural in shape and in size When the T wave in the electrocardiogram becomes deformed even in a limited way some degree of cardiac enlargement is common As the condition progresses such enlargement assumes prominence and hilar clouding makes its appearance as evidence that heart failure has set in (Figs 1 and 2) Sometimes the cardiac silhouette is large because of the addition of pericardial effusion If a beriberi syndrome has developed much pulmonary congestion may show in the absence of conspicuous cardiac enlargement

The beriberi syndrome In those patients who consume large quantities of alcohol especially in the form of beer to the exclusion of regular and adequate meals the body is supplied with a surfeit of calories from a high intake of carbohydrates but is deficient in vitamin B Thus a clinical syndrome results in the occident similar to that styled as beriberi in the orient one which develops when polished rice forms the staple article of diet

The clinical features arising from such thiamine deficiency include the accumulation of fluid in serous cavities anasarca warm skin a pounding arterial pulse with a raised pulse pressure and increased circulation time characterizing the so-called *high output* heart failure At the height of the illness the electrocardiogram may be surprisingly normal but as soon as satisfactory diuresis and clinical improvement take place after treatment with thiamine the tracing usually shows sharp and temporary inversion of T waves Presumably such characteristic fugitive changes result from an abrupt mobilization of electrolytes within the myocardium after the beneficial action of thiamine

The purpose of this paper however is to emphasize the rarity of this beriberi syndrome among those who drink spirits in excess at least in my own country and to name this circumstance as among the chief reasons for our erstwhile neglect to



Fig 2 Great enlargement of the heart hiding the hilar congestion.

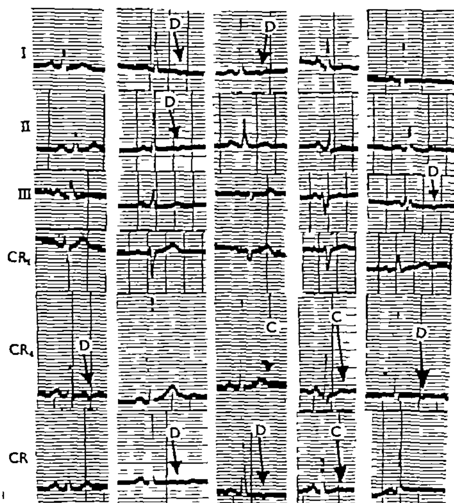


Fig. 6. The electrocardiogram in five patients showing cloven (*C*), dimple (*D*) and low T waves.

which is somewhat subdued in height and is usually seen in Leads I, II or CR_4 (*C* in Figs. 5 and 6). It is known that a cloven T wave may appear in the apical lead in healthy children, but in this event the T is deformed to a greater extent in the right ventricular lead. Rarely the cloven T may be the outcome of a very limited cardiac infarction, but in practice it may be assumed that this deformity of the T in left ventricular leads in a patient without chest pain signals the diagnosis of alcoholic cardiomyopathy, and its presence should direct inquiry into the amount of spirits habitually consumed. A cloven T can remain apparent in the presence of fibrillation, provided that the effects of neither digitalis nor transient bundle branch block have been added. *Abstinence from spirit drinking may* cause this distinctive electrocardiographic sign to disappear in concert with loss of all symptoms (Fig. 7).

THE DIMPLE T WAVE. Herein lies another characteristic electrocardiographic deformity in early alcoholic affection of the myocardium. The S-U period is isoelectric except for an interruption by a shallow and narrow dimple (*D in Figs. 5 and 6*). This dimple T is commonly found in Leads I and CR_7, and sometimes in Lead CR_4.

Occasionally a dimple T has appeared in young subjects after a meal, but this postprandial electrocardiographic change disappears in the course of a few hours. Should the sign be met with rarely in a patient with cardiac pain, it is never a lone abnormality and it occurs alongside more obvious changes in other leads, including

significant Q waves deep and wide T wave inversion and depression of the S T segment

When either cloven or dimple T waves are exhibited T waves in other leads are often of low voltage

FRANK T WAVE INVERSION With the passage of time and the spread afield of myocardial fibrosis the newly described distinctive deformity of the T wave in certain leads may be accompanied by deeper inversion of the T wave in other leads but even in this circumstance the base of the T wave is not so wide as in those patients in whom the electrocardiogram signifies cardiac infarction from coronary arterial disease (Fig 8)

Arrhythmia

EXTRASYSTOLES When the clinical features of alcoholic cardiomyopathy were described earlier emphasis was given to the presence of extrasystoles in the company of tachycardia The electrocardiogram in this instance in addition to confirming the rather unusual combination shows that the frequent premature beats commonly take origin from multiple foci in the heart (Fig 9)

PAROXYSMAL TACHYCARDIA Because this innocent rhythm is so often exhibited in healthy subjects care should be taken before attributing it to heavy spirit-drinking Nonetheless when auricular tachycardia appears for the first time in an adult male alcoholic cardiomyopathy should be kept in mind as a possible cause and the distinctive electrocardiographic signs should be sought whenever sinus rhythm is resumed

AURICULAR FIBRILLATION When the common causes of fibrillation like mitral stenosis thyroid toxemia cardiac infarction hypertension and constrictive pericarditis have been excluded in a given patient it should be known that it may often assume one of two other forms namely the lone kind of fibrillation or one which has its source in alcoholic cardiomyopathy The latter can be told from the former by the quicker heart rate the association of some degree of cardiac enlargement and the presence of one of the distinctive T wave changes or multifocal extrasystoles in the electrocardiogram (Fig 10)

To bear in mind excessive spirit drinking as the cause of paroxysmal or established auricular fibrillation in the adult and to examine the electrocardiogram critically before digitalization has deformed it is to re emphasize the common incidence of alcoholic cardiomyopathy

Faulty conduction Mention has already been made when description of the sparse pathologic changes in alcoholic cardiomyopathy was made that one or more of the scattered fibrotic areas may lie astride the path of the conducting tissue Indeed bundle branch block first as a transient feature and later as a permanent fault is

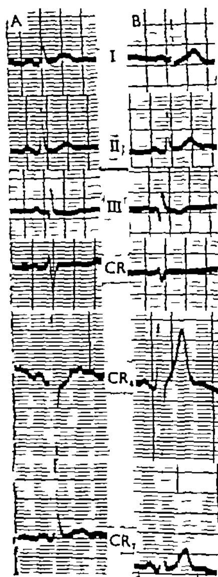


Fig 7 The cloven T [illegible] es in Leads CR_4 and CR [illegible] in 1 are absent from *B* which was recorded after complete abstinence from spirit-drinking

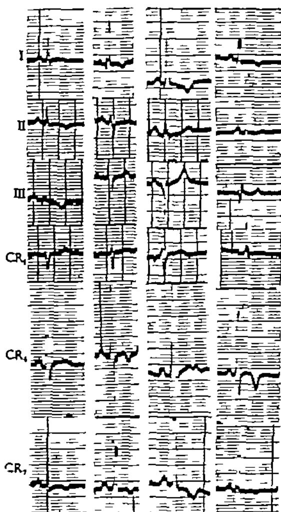


Fig 8 Electrocardiograms from four patients in which cloven and dimple T waves are associated with frank inversion of the T in certain leads There was considerable enlargement of the heart in each patient

not uncommon in patients addicted to spirit drinking through many years

When the block is transient one of the characteristic deformities of the T wave may be present in the standard electrocardiogram recorded when the block is absent (Fig 11)

Examples of complete heart block although less common than those exhibiting bundle branch block are also not infrequently met with

THE $S_1S_2S_3$ PATTERN Recently we have shown that when the S wave in Leads II and III exceeds the R wave in the absence of an S in Lead I a lesion is present in the anterolateral portion of the left ventricle Naturally the common cause of this fault is cardiac infarction from coronary arterial disease but some other kind of cardiomyopathy may also supply the source When it arises from alcoholic cardiomyopathy a widening of the QRS complex may be an associated finding (Fig 12)

The beriberi electrocardiogram Mention has already been made of the fugitive T wave inversion which takes place when alcoholism has produced a beriberi syndrome and which appears immediately in the wake of thiamine therapy reverting to normal in concert with the benefit which such therapy induces

General remarks

Now that the clinical pathologic and electrocardiographic features of alcoholic cardiomyopathy have been described some general questions remain to be considered which relate to the patient and his work and habits

What kind of man is he? He is usually a male and past middle age As a rule he meets his physician in private rather than in hospital practice He is neither an outcast of society a sloth in commerce nor a *sluggard in industry On the other hand* he is sociable and likable loyal to his colleagues and superiors and a restless worker Day in and day out he canvasses custom and hawks his ware as he fills and refills his guest s goblet and his own On his return home he delves into the accumulated work of the day fortifying himself far into the night from the bottle at his side For a time the stimulant appears to stimulate his mind in a longer time it poisons his heart and he becomes a slave and the victim of the merciless competition inseparable from twentieth century commercialism

Sometimes he is the unhappy husband who becoming estranged to his home prefers to spend his evenings at the club or the bar thereby avoiding the just admonishment of his wife who sees more clearly than he does the approaching doom in that through his stubborn disbelief that there is anything wrong he is not impelled to modify his drinking habits

Although he often plays at golf he never excels at it for he is more attracted to the amenities of the clubhouse than to improving his game Another might be an ag

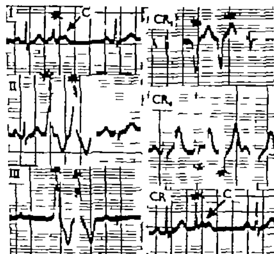


Fig 9 Multiple extrasystoles ( ) and moderate tachycardia. Cloven T waves (C) in two auricular extrasystoles

bachelor without hobbies who whiles away his hours of loneliness and as he attempts to uplift his depressed spirits with alcohol he drains his cup of sorrow in the false hope of removing his own

Not infrequently a patient's occupational association with the liquor trade as distiller or sampler merchant or publican brings to him an easy access to alcohol and to a habit which he tries in vain to resist or restrict

How much does he drink? It is not difficult to ascertain the kind of alcohol consumed by patients presenting with alcoholic cardiomyopathy and the order of preference proved to be whisky gin rum brandy and wine. Naturally these were often taken in combination. If the consumption of alcohol was confined to beer the syndrome described here was not met with but of course beer was often taken in addition to spirits. When habitual excessive drinking is confined to beer the beriberi syndrome is the likely manner in which the clinical picture presents itself

An accurate estimate of the amount of alcohol consumed by individual patients however is seldom obtained. Nonetheless persistent interrogation which uses finesse and artifice when the meagerness of the admitted daily intake for instance is deliberately derided at first may draw a confession to taking larger quantities and permit a truer view of the situation. Indeed when the patient capitulates to this subtle questioning he might resort to boastfulness and brag as one did "I have taken two bottles of whisky each day for more than five years and I have never once been drunk". It is constant drinking not spasmodic inebriation that poisons the heart. Another ruse which the interrogator armed with trust in the electrocardiographic clue can often use to extract from a patient a confession to drinking in excess of what he first names is to instruct the patient to abstain from drinking any alcohol because it is damaging the heart muscle adding that since he only partakes of small quantities he would doubtless find it easy to conform with the request. This brings an admission that he does drink substantial quantities and an appeal that a modified ration be allowed. At all times the ingenuity of the interrogator is pitted against the craftiness of the patient. In one such instance in which the interview had failed to draw an admission as the patient turned to don his coat a bulging hip pocket came into view and subsequently was made the object of inquiry when a flask of brandy was uncovered and was acknowledged to be a constant companion. Of course the physician's reliable ally in his search for a true history is the spouse unless in rare in

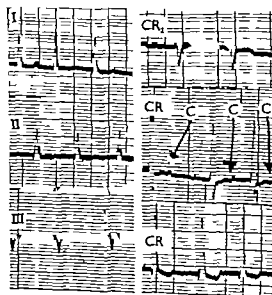


Fig 10 Cloven T waves (C) are apparent in Lead CR in spite of the effects of digitalization in patient with auricular fibrillation

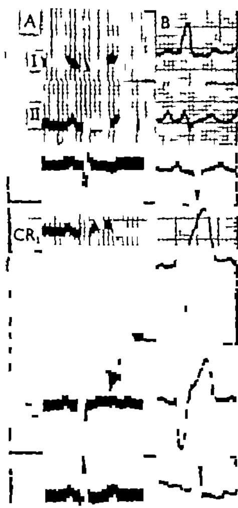


Fig 11 A down T wave (C) in Lead CR in A is absent in B where left bundle branch block has supervened

stances the two are in collusion because of habits shared

Although the electrocardiographic signs described here contribute to the recognition of alcoholic cardiomyopathy they too cannot measure the quantity of alcohol which can produce the myocardial changes Inseparable from the search for data that might provide information on the cardiotoxic dosage of alcohol is the appreciation that patients exhibit a different degree of tolerance to its deleterious effects so that it is difficult to pronounce on what is enough and harmless and what is excessive and harmful To prejudge susceptibility in this context is not within the physician s competence It is certain however that a daily consumption of 6 to 12 portions of spirits will produce cardiomyopathy in as many years and in far less time in susceptible patients

To most the cost of the commodity is prohibitive and for this reason alcoholic cardiomyopathy is less common among hospital than private patients but the privilege of occupation whereby its cost might be debited to a business expense account or its ready availability through the nature of one s work or trade may make its actual cost a matter of less consequence Those who crave spirits and through financial sacrifice procure it may share the sentiment of one patient who when asked how he afforded it replied Doctor you don t regard whisky at 37/6 (thirty seven shillings and sixpence) a bottle is expensive when you have to pay 1/4 (one shilling and fourpence) for a cauliflower

Treatment

This investigation does not permit one to moralize in regard to a national habit just because it is being abused nor does it justify a plea to forgo a conventional custom of entertaining a friend to casual drinks at a bar at table or in the home It is concerned not with the consumption of alcohol as a sin to flee from but with alcoholism as a dread disease to avoid Its treatment is considered under three heads namely its prevention and the management of the illness during its early and late phases

Prevention Prevention of alcoholic cardiomyopathy can only be effected through applied education and wholesale dissemination of information about the injury to the heart which *inevitably follows habitual* spirit drinking This should become a national responsibility because it is of national concern Because the habit is commonly formed in young adult life arrangements for the matter to be clearly discussed in higher schools colleges and universities should become custom and it must find a place in *the official scholastic curriculum* Organized lectures need to be inaugurated among industrial and commercial societies for it is in these groups that the habit so commonly finds first root To be forewarned is to be forearmed and prevention is better than cure may both be hackneyed

phrases but none can be more apt in a discussion of the treatment of alcoholic cardiomyopathy Nor must medical opinion stand aloof to the problem of preventing this scourge of habitual excessive spirit drinking whose ravages on the heart have only recently come to light Warning of its dangers must be tendered early Such advice given and accepted will gain well earned satisfaction Advice given and thwarted will bring disappointment though without guilt to its counsellor Advice withheld breeds guilt and remorse in that a duty has been neglected and an opportunity has passed

The early phase The early stage is identified when a patient presents with light symptoms like moderate breathlessness or palpitation and when characteristic signs in the electrocardiogram tell of the sparse changes in the myocardium and the heart at cardioscopy shows only minimal or no cardiac enlargement At this point the amber light has winked and the signal is at red and failure to halt means a crash on the journey ahead Advice to the patient must be sharp and peremptory conveyed to him as a telling command in words implying total abstinence At the start the patient often reacts indifferently to this strict injunction for he regards nature as the villain that produces disease and he is used to hire a doctor to cure it so that he takes exception to a suggestion that the discomfort he suffers has been wrought *at his own hand* When he is in this petulant mood it takes time and patience to convince him of the seriousness of his illness Even when he bends in understanding he continues to plead for a reduced ration of the spirits which he has been told are poison to him but the physician must stand firm for nothing short of complete weaning will halt the march of the cardiac fibrosis

Because the patient is usually overweight his adherence to a reducing diet is to be urged in the knowledge that he cannot lessen his grossness without foregoing alcohol

The late phase The late stage is recognized when breathlessness is a prominent symptom and when the heart shows considerable enlargement with characteristic signs of heart failure More severe changes have taken place in the myocardium and the damage now is irretrievable Because the characteristic signs in the electrocardiogram have been obscured by greater

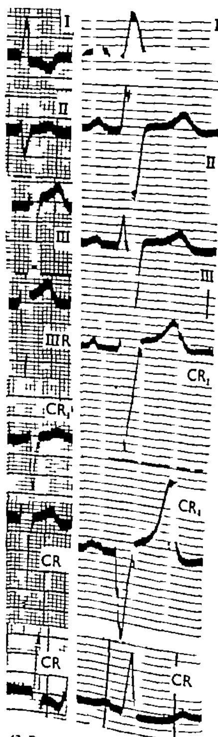


Fig 12 Deep S ... in Leads II and III ... in Lead I in 2 patients QRS is a little wide

deformities heart failure from coronary arterial disease is often mistakenly diagnosed for alcoholic cardiomyopathy

Treatment here has no high aspiration and it is directed solely to the relief of the symptoms of heart failure Thus the intake of salt and fluid is restricted and digitalis is prescribed along with oral diuretics Thiamine should be added if a beriberi syndrome has supervened

At its best however therapy at this stage can be little more than a palliative arrangement for the opportunity to do real good has passed This realization should spur effort to conclude an early diagnosis in order to introduce treatment before hope of recovery has faded

Summary

Alcoholic cardiomyopathy is a common condition and there are many reasons why our acceptance of this truth has been so long delayed First the stealth with which the condition sets in has made its recognition difficult Next the clinician has been accustomed to watch the deleterious effects of alcohol on the liver in the shape of fibrosis and on the mind in the form of delirium tremens and has been inattentive to its cardiotoxic effects unless these presented as the rare syndrome of beriberi Again the sparsity hitherto of signs which give proof that heavy spirit drinking has caused heart failure especially when a history of such overindulgence has been carefully concealed has frustrated a true diagnosis Moreover whenever the electrocardiographic changes here attributed to alcoholic cardiomyopathy have been discovered in a patient with or without chest pain they have too often been wrongly attributed to coronary arterial disease Similarly an abnormal rhythm like auricular fibrillation when unassociated with one of its common causes has been regarded too readily as arising from coronary disease

The patient more often male than female is about middle age and often a successful man of business As a rule he is overweight and this is often accepted as the cause of his moderate breathlessness which is the most common presenting symptom If palpitation should be the chief complaint extrasystoles may be discovered alongside a moderate tachycardia or the arrhythmia may take the form of paroxysmal or established auricular fibrillation Other signs of cardio arterial derangement are sparse or absent although radiologically some slight enlargement of the heart may be detected

During this early phase of the illness when the changes in the myocardium are limited and scattered the electrocardiogram can be a princely test for it will show distinctive signs which compel a more persistent questioning of the patient in regard to his drinking habits Such electrocardiographic signs include some form of arrhythmia like extrasystoles which are usually multiple and arise from diverse foci and occur *in the presence of a moderate* tachycardia or auricular fibrillation The T waves are deformed in a distinctive way presenting a spinous cloven or dimple design patterns which are not seen by themselves in the electrocardiogram of coronary arterial disease Recognition of the illness at this stage is rewarding because abstinence from spirit drinking can halt the march of fibrosis in the myocardium and restore the patient to his customary health

To miss the diagnosis or to ignore advice on complete abstinence from spirit drinking leads inevitably to the more serious phase of the illness from more prolific myocardial fibrosis In this event breathlessness has progressed to become a menacing symptom and the more obvious signs of heart failure make their appearance These include a prominent venous pulse systolic murmurs from mitral and tricuspid regurgitation triple heart rhythm considerable cardiac enlargement pulmonary congestion hepatic distention and edema The ECG changes are now more obvious and the earlier distinctive T wave patterns are submerged either by an arrhythmia bundle branch block complete heart block or by a more frank inversion of the T An $S_1S_2S_3$ pattern is often added Treatment in this circumstance can only be palliative in nature and directed to the alleviation of heart failure for complete abstinence from spirit drinking cannot alter the substantial myocardial changes Thus digitalization oral diuretics restricted intake of fluid and sodium and thiamine if the syndrome of beriberi has been added are the orthodox remedies to be given but without hope of producing lasting improvement

The salutary lessons collected from a study of alcoholic cardiomyopathy are that the condition is common and that it commonly goes unrecognized until it reaches a stage at which the myocardial fibrosis can neither be halted nor improved by any form of treatment. In the early phase of the illness abstinence from spirit drinking can arrest the myocardial injury. Clearly, therefore, the need is for early recognition of the condition, when attention to its distinctive electrocardiogram will make this possible.

REFERENCES

A bibliography covering this paper is found elsewhere (Evans W. Brit. Heart J. 21 445 1959)

Annotations

On the neglected role of water and potassium in cardiovascular therapy

The use of low sodium diets diuretics and digitalis occupies time honored and rather well-defined role in the therapy of cardiac pate ts However in spite of the gorous and correct use of such methods the general practitioner as well as the consulting cardiologists is all too often faced with patients who are seemingly refractory to all types of currently accepted medical nd surgical therapy

The matter of how much water to allow the cardiac patient is much less clear nd the marked restriction of w ter has been questioned by several workers The majority of physicians probably permit patients with cardiac problems to take liquids ad libitum The intake of w ter is then dependent on the sensation of thirst which varies from patient to patient is influenced by habit and environmental circumstances nd may even be depressed because of cardia failure This permissiv pproach usually means that the volume of liquids imbibed is much less tha the minimum require ment for the optimal limination of the retained sodium and w ter There ha been studies which demonstrated that the olume of liquid imbibed during a low sodium regimen a most important factor in the results obtained

I regard to potassium considerable literature has accumulated indicating that in cardiac failure there is u ually a intracellular deficit of potassium even though the level of serum potassium seem to be normal Selye[7] has suggested experimentally that potas ium exerts a protecti role on the myo cardium Furthermore successful diures causes added loss of potassium particularly if the newer saluretic drugs are used Thus t quite possible that potassium too may be an importa t part of the therapy of every cardiac patient with due regard to the renal involvement present

Recently a report was made of the experience of several years with a large group of patients in whom careful ttention was paid to the intake of w ter nd the supplementary use of potassium The regimen evolved is quite similar to that generally accepted for cardiac patients in terms of restriction of sodium and adequate intake of protein The essential difference is in the fact that water was ctually prescribed in each case in amounts which usually averaged between 2 500 nd 3 000 c daily as natural water This high intake of water is similar in amount to that used in the studies previously alluded t and in our experience much higher than the intake in the patient who is allowed water ad libitum.

Potassium chloride 1 5 to 3 Gm was also given daily d vided doses Levels of serum potassium were maintained bove 4 2 mEq per liter since t levels below this alue electrocardiographic signs of low potassium extrasystoles and paroxysmal tachycardias were often encountered W believe therefore that the commonly used lower limit of normal of serum potassium e 3 7 mEq per liter may represent hypopotassemia for cardiac patients

This pproach was used with surprising nd gratifying clinical success in practically all types of cardiac in olvement cardiac failure (particularly the refractory type) hypertensio angina pectoris and chronic cor pulmonale I many nstances t was possible to decrease nd even discontinue the use of diuretics digitali and the arious hypoten sive agents Most mportant of all the patient weight nd sense of improvement were the major parameters of successful use of the regimen Natu rally some practice on the part of the physician is necessary to titrate each individual case as is an acquaintance with some of the reasons for seeming failure as detailed in the report

Resano[8] has independently studied group of 26 cardiac patients in great detail using the principle of this regimen His findings are extremely interest ing not only because he was able to achiev success but because of his observations If the intake of water was kept at levels of 1 500 to 2 000 c then intake and output were approximately equal How ever when he increased the intake of water of his patients to 2 500 c he achieved diuresis of at least 3 000 c c or in other words output exceeded intake by 500 c Finally at these levels of higher intake he did not observ the so-called dilution syndrome

These findings make it ppear likely that water and potassium are of more alue in the therapeutic armamentarium for cardiovascular disease than is commonly realized It is suggested that the observations on the ad libitum use of w ter as well as the benefits to be derived from a higher intake of water by patients with cardiovascular di ease can be easily checked by almost any physician who sees general medical cases Finally more studies are needed in order to clearly delineate the usefulness and mechanisms of the low sodium high water high potassium regimen

Demetrio Sod Pallares M D
Burton J Polansky M D
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REFERENCES

1 Bridges W C Wheeler E C and White P D Low sodium diet and free fluid intake in the treatment of congestive heart failure New England J Med 231 573 1946
2 Lewy C M Strazza J A and Jaffin A E Fluids in congestive heart failure J A M A 231 1120 1946
3 Schemm F R High fluid intake in the management of edema especially cardiac edema the details and basis of the regimen Ann Int Med 17 452 1945
4 Wolf A V Dehydrating effect of continuously administered water Am J Physiol 143 567 1945
5 Gorham L W et al The relative importance of dietary sodium chloride and water intake in cardiac edema Ann Int Med 27 575 1947
6 Pitts R F The physiological basis of diuretic therapy Springfield Ill 1959 Charles C Thomas Publisher
7 Selye H Chemical prevention of cardiac necrosis New York 1959 Ronald Press Company
8 Sodi Pallares D et al A low sodium high water high potassium regimen in the successful management of some cardiovascular diseases Preliminary clinical report Canad M A J 83 243 1960
9 Reano-Perez F J Valoracion del regimen hiposódico-hiperhídrico en algunos padecimientos cardiovasculares Thesis Facultad de Medicina Universidad Nacional Autónoma de México 1960

Significance of reticuloendothelial cells in atherosclerosis

The relationship between lipid metabolism and atherosclerosis has led to investigations into the part played by cells of the reticuloendothelial system in both these processes It has been thought for many years that reticuloendothelial cells may be involved in lipid metabolism and the presence of macrophages in plaques in the walls of blood vessels suggests that these cells may also be important in the pathology of atherosclerosis Recent work indicates that Kupffer cells of the liver and the tissue macrophages may influence the development of experimental atherosclerosis in two distinct ways

It appears that the Kupffer cells may have some special role in removing cholesterol from the blood stream After the feeding of cholesterol to or the intravenous injection of turbid hypercholesterolemic serum into rats the Kupffer cells were found to be filled with cholesterol These cells have also been shown to have a significantly higher content of cholesterol and cholesterol ester than do the hepatic parenchymal cells The breakdown and subsequent excretion of cholesterol also appears to be related to the activity of the Kupffer cells In rats fed on high fat high-cholesterol diet it has been found that if the activity of the reticuloendothelial system is stimulated by intravenous injections of zymosan the levels of cholesterol cholesterol ester and triglycerides in the plasma and liver are significantly lower than in control animals These findings suggest that the concentration of cholesterol in the plasma and other tissues may be related to the activity of the Kupffer cells

In regard to the atherosclerotic lesion itself macrophage cells filled with lipid have been shown to attach themselves specifically to areas of the aorta overlying atheromatous plaques These cells have been seen passing through the aortic endothelium in cholesterol fed rabbits It is not known whether these macrophages are in the process of leaving the blood stream or whether they are being mobilized from within the arterial wall

It may be that macrophages play some part in preventing the accumulation of lipids in the tissues Macrophages could do this in two ways They could ingest the material and transport it to some other site such as the lungs or the gut where it may be excreted or they could take up the lipid and metabolise it themselves The movement of lipid filled macrophages into or out of the arterial wall has been mentioned In ear chambers which were established in cholesterol fed rabbits macrophages have been seen lying alongside the growing tips of blood capillaries and these cells exhibit the characteristic birefringence associated with the spherocrystals of cholesterol when cholesterol is seen under polarized light Reticular cells in lymph nodes also take up and store cholesterol and cholesterol esters readily

Once in the macrophage the lipids are exposed to the enzyme systems of the cell Histologically macrophages that have taken up cholesterol show an increased sudanophilia after a few days This change is associated with the accumulation of fatty acids within the cells Cholesterol can be esterified and cholesterol esters can be hydrolysed by macrophages and these cells are also capable of hydrolyzing and oxidizing triglycerides and fatty acids to carbon dioxide and water[10] The exact significance of these transformations is not yet known but they may be related in some way to the role of these cells in removing lipids which accumulate in relatively avascular areas of the body

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REFERENCES

1 Gilbert A and Jomier J La cell le étoilee du foie Arch de med exper et d anat path Paris 20 145 1908
2 Jaff R H and Berman S L The relations between Kupffer cell and liver cell Arch Path 5 1020 1928
3 Byers S O St George S and Friedman M Hepatic reticuloendothelial cell as participants in the normal d position of exogenous cholesterol in the rat *In* Physiopathology of the reticuloendothelial system Oxford 1957 Blackwell Scientific Publications
4 Di Luzio N R Lipid composition of Kupffer cell Am J Physiol 196 884 1959
5 Di Luzio N R Reticuloendothelial involvment in lipid metabolism Ann New York Acad Sc 88 244 1960
6 Poole J C F and Florey H W Changes in the endothelium of the aorta and the behavior of macrophages in experimental atheroma of rabbits J Path & Bact 75 245 1958
7 Sanders A G and French J E Capillary permeability in relation to atherosclerosis *In* Factors regulating blood flow edited by G P Fulton and B Zweifach Washington D C 1958 American Physiological Society
8 French J E and Morris B The uptake and storage of lipid particles lymph glands in the rat J Path & Bact 79 11 1960
9 Day A J and French J E The synthesis and hydrolysis of cholesterol ester by cells of the reticuloendothelial system Quart J Exper Physiol 44 239 1959
10 Day A J Oxidation of ¹⁴C labeled chylomicron fat and C labeled unesterified fatty acids by macrophages in vitro and the effect of clearing factor Quart J Exper Physiol 45 220 1960

Pulmonary second sound in the tetralogy of Fallot

The second heart sound in the pulmonary area in patients with cyanotic tetralogy of Fallot is single and produced by closure of the aortic valve (A_2) the pulmonary element being inaudible and only rarely recorded in the phonocardiogram.[1-4] It has been suggested that the absence of the pulmonary component (P_2) in Fallot tetralogy is due to low levels of pulmonary flow most of the right ventricular output being shunted to the systemic circulation This was supported by the appearance of P_2 after pulmonary valvotomy or Blalock pulmonary anastomosis when the pulmonary flow increases and by not uncommonly recording P_2 in the so-called acyanotic tetralogy in which the pulmonary flow is not diminished Comparison of the magnitude of pulmonary flow of patients with pulmonary stenosis and that of patients with Fallot tetralogy shows that it may be quite low in cases of severe pulmonary stenosis and comparable to the levels observed in the average case of cyanotic tetralogy In severe pulmonary stenosis however P_2 is not uncommonly recorded Investigation of the effect of norepinephrine in pulmonary stenosis and the tetralogy showed that accentuation of P_2 or its appearance on the phonocardiogram if it was not recorded prior to the administration of the amine will frequently occur in severe pulmonary stenosis but not in the tetralogy It seems likely therefore that other factors in addition to pressure (and flow) are responsible for the absence of P_2 in the tetralogy Such factors may be (a) deformity of the pulmonary valve and hypoplastic main pulmonary artery resulting in inadequate cusp excursion toward the closed position (b) dorsal displacement of the pulmonary valve and artery accompanying the aortic override In view of the poor conduction of sound through the lung tissue[8] this results in attenuation of P_2 whereas the frontal position of the aorta is held responsible for the loud A_2 Maximal dorsal displacement of the pulmonary valve is encountered in transposition of the great vessels absence of P_2 with loud A_2 has in fact been described in transposition with pulmonary stenosis[10] Absence of P_2 is also noted in transposition with increased pulmonary flow and normal pulmonary arterial pressure[11] Conversely absence of aortic override is probably at least in part responsible for the audible P_2 in several cases of acyanotic tetralogy As a final point it may be mentioned that when distance is not involved as in intracardiac phonocardiograms P_2 is invariably recorded in patients with the tetralogy[12]

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REFERENCES

1 Vogelpoel L and Schrire V The role of auscultation in the differentiation of Fallot tetralogy from severe pulmonary stenosis with intact ventricular septum and left to right shunt Circulation 11 794 1955
2 Leatham A and Weitzman D Auscultatory and phonocardiographic signs of pulmonary stenosis Brit Heart J 19 303 1957
3 Castle R F and Craige E Auscultation of the heart in infants and children Pediatrics 26 511 1960
4 Gardiner J M The phonocardiogram in con

genital heart disease Australasian Ann Med 8:225 1959
5 Leatham A. Heart sounds and murmurs in ventricular septal defect Guy's Hosp Rep 108:361 1959
6 Kjellberg S R Mannheimer E Rudhe U and Jonsson B Diagnosis of congenital heart disease Chicago 1959 The Year Book Publishers Inc
7 Boutsaros G A The effect of norepinephrine on the phonocardiogram and hemodynamics of congenital and acquired heart disease (In preparation)
8 McKusick V A Cardiovascular sound in health and disease Baltimore 1958 Williams & Wilkins Company
9 Wood P Diseases of the heart and circulation London 1956 Eyre & Spottiswoode
10 Cleland W P Goodwin J F Steiner R E and Zoob M Transposition of the aorta and pulmonary artery with pulmonary stenosis Am Heart J 54:10 1957
11 Boutsaros G A Unpublished observation
12 Feruglio G A and Gunton R W Intracardiac phonocardiography in ventricular septal defect Circulation 21:49 1960

Medicine versus science

The goal of science is the discovery of truth whereas the goal of medicine is the prevention and cure of disease many times these two goals can be harmonized and science can be harnessed to serve medicine but there are conflicts and the issues in such conflicts should be made as clear as possible

It is often said for example that the burden of proof rests with the physician who states that a drug or form of treatment is beneficial in certain disease and in a scientific sense this is justified If the implication however that all physicians should withhold such treatment until proof of its efficacy is incontrovertible equally justified Such a position is in accord with the traditions of science but it may sometimes be challenged from the point of view of medicine

Suppose for example that a new drug is available for the treatment of a chronic disease Suppose also that it has been demonstrated that its short term and even long term side actions are negligible and that it is not demonstrably toxic Suppose also that the disease it is purported to control is not only productive of morbidity but potentially lethal and that because of its chronicity an incontrovertible answer with reference to efficacy of drug therapy will not be available for 15 to 20 years Where is the moral burden here from the point of view of medicine and its goal Is it justified to withhold such treatment in the name of science

It seems to me that when there is a reasonable chance that a form of treatment may be effective and if there are not demonstrable adverse effects the patient should be given the benefit of doubt The saving of life is more important than proving a point On the other hand if the doubt as to efficacy is strong enough and the evidence as to lack of toxicity is weak enough such treatment should be withheld This is one of the areas in which the erudition and judgment of the individual physician has its greatest exercise There is a region of doubt in this area moreover where the scientific evaluation of the efficacy of treatment in a controlled experiment involving the placebo exhibition as well as the withholding of the drug is needed and justifiable It cannot be overemphasized however that for the individual physician the decision to prescribe or not to prescribe may be a moral one pending rigid scientific proof or disproof of the efficacy of a drug If the goal of science has been attained and such evidence is available there is no conflict In the interim however the goal of medicine must still be pursued

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The kinked left innominate vein

A certain charm lies in original observations about simple phenomena especially when these must have been seen repeatedly but passed unnoticed by others In 1935 L G Sabathie drew attention to engorgement of the left external jugular vein as a new signo periferico en las aortopatias

However the sign and Sabathie's observations of it appear to have largely escaped the notice of English speaking cardiologists until 1960 when K S Smith[1] described the significance of the kinked left innominate vein and G Lasta drew attention to the priority of Sabathie[2]

Both Sabathié and Smith published convincing photographs of unilateral or predominantly unilateral engorgement of the left external jugular vein. Theoretically, the anatomic disposition of the left innominate vein makes it easy to understand how the vein might be compressed should the aortic arch rise higher than its usual position. Pertinent here is the relatively low pressure of blood in the thin-walled innominate vein and the anterior location of the vessel close to the bony thorax where it may readily be compressed by any expanding structure including a aortic arch. High arterial pressure may displace the aortic arch upward and unfold it, whereas arteriosclerosis may allow elongation even in the absence of hypertension. Similar changes in the arterial trunks that spring from the arch behind the left innominate vein may contribute to the compression. A rigid aortic arch, often found with atheroma and calcification, is more likely to interfere with neighboring venous flow than is an aorta dilated dynamically and exerting only intermittent pressure.

All five of Smith's published cases had arterial hypertension and radiographs indicated an abnormally high aortic arch plus either unfolding or obvious atheroma. There was no evidence of other cause of left innominate vein obstruction. Venous pressure measurements showed elevation in the venous system of the left arm as well as the left side of the neck, indicating obstruction proximal to the junction of subclavian and innominate veins. Sabathie had also recorded similar radiographic findings in such cases and noted that the venous pressure in the left antecubital vein was higher than that in the right.

Smith pointed out that the unilateral engorgement of the left external jugular vein as a sign of a kinked left innominate vein is in some ways a counterpart of the kinked right common carotid artery described by Parkinson and Bedford, both signs being attributed to a high and probably rigid aortic arch. Clinically, a systolic thrust or pulsation visible or palpable at the upper chest or suprasternal notch may permit diagnosis of an enlarged or elongated aortic arch. Otherwise there are few dependable signs. The kinked right carotid artery is a valuable sign but is almost entirely confined to women. The unilateral engorgement of the left external jugular vein is an additional important piece of evidence and is found as often in men as in women. Both Sabathié and Smith admitted that other causes of obstruction of the left innominate vein could also produce the sign, for example, neoplasm.

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REFERENCES

1. Sabathié, L. G.: Un nuevo signo periférico en las aortopatías, Archivos de medicina interna 1:325, 1935.
2. Smith, K. S.: The kinked innominate vein, Brit. Heart J. 22:110, 1960.
3. Lista, G.: Kinked innominate vein (Letter), Brit. M. J. 2:536, 1960.
4. Parkinson, J., Bedford, D. E., and Almond, S.: The kinked carotid artery that simulates aneurysm, Brit. Heart J. 1:345, 1939.

Book reviews

VISUAL AIDS IN CARDIOLOGIC DIAGNOSIS AND TREATMENT Edited by Arthur M Master Consultant in Cardiology The Mt Sinai Hospital New York Chairman Cardiovascular Disease Section Committee on Scientific Program American College of Chest Physicians June 1959 and Ephraim Donoso M D Research Assistant in Cardiology The Mt Sinai Hospital New York New York 1960 Grune & Stratton Inc 216 pages Price $10

Merlin had the difficult task of building up the magical powers of the sword Excalibur without detracting from its wielder King Arthur His aim was to make the King appear fortunately blessed in possessing such weapon but also neither unskillful nor naive in trusting the magic blade The editors and authors of this volume are faced with an analogous difficulty in crediting instrumental advance without discrediting clinical acumen

There are several well written well illustrated chapters which can serve as concise reference summaries for the general medical reader—specifically those chapters on shunt localization by indicator-dilution techniques angiocardiography and selective angiocardiography As may be expected in collection originating from symposium there are also filler chapters of only transient worth Chapters of intermediate quality are concerned largely with defining or exercising the special vocabularies in the different areas of cardiographic or cardiologic interest (In this connection the published recommendations of the New York Heart Association as to nomenclature did not influence the choice of terms in the phonocardiographic discussion of valvular regurgitation) One item which will provoke the curiosity or skepticism of physicians is the mere mention of pathognomonic third sound detected in the right ventricular phonocardiogram in constrictive pericarditis no discussion or explanation of the distinctive nature of the finding is given

So many of the authors saluted the organized team that this reader has come to hope that further aids and advances in cardiologic diagnosis and treatment will permit a return of emphasis toward heightened individual competence and away from a feudal division of cerebration and responsibility

CARDIOVASCULAR DISEASES By David Scherf M D F.A C P Professor of Clinical Medicine New York Medical College Flower and Fifth Avenue Hospitals and Linn J Boyd M D F A C P Professor and Director of Medicine Flower and Fifth Avenue Hospital New York Third edition New York 1958 Grune & Stratton Inc 829 pages Price $18.50

It has been nearly ten years since the second edition of this textbook appeared and during that time great strides in medical progress have been made Not the least of these advances has been in cardiology such as electrocardiography cardiac catheterization angiocardiography and the diagnostic enzymes The book is written with emphasis on historical data physical diagnosis and clinical judgment and this is certainly worth while but it is unfortunate that more detail was not devoted to these more recent diagnostic procedures

The paucity of electrocardiographic illustrations is shortcoming and the reader is told that he must purchase the authors text on that subject for more comprehensive information Some of the electrocardiograms shown are not labeled and as such may be confusing Much of the information is derived from the wide and varied experience of the authors and is written from such standpoint in style that is enjoyable and easily read There is extensive bibliography with complete titles and many classic articles are included

In work covering the broad field of cardiovascular disease there are bound to be ideas that will not meet general agreement The authors awareness of this is indicated in the statement When the use of leeches is recommended one often encounters smile of pity The use of leeches is suggested for acute engorgement of the liver in congestive heart failure and thrombophlebitis In light of more recent therapeutic agents this hardly seems necessary Despite these objections and a few others the book covers the field of cardiovascular disease in an informative and entertaining manner Students and interns will find the book useful but it is not recommended for specialists in the field

Announcements

The University of Colorado School of Medicine announces the COCHEMS COMPETITION fund for which were provided in the will of the late Mrs. Jane Nugent Cochems. A prize of $2,500 will be awarded to the author of the best paper on the subject of "The Diagnosis, Etiology and Treatment of Thrombophlebitis." The competition is open to all physicians, and entries must be received in triplicate on or before Oct. 1, 1961.

The Colorado National Bank of Denver, Trustee under the will of Jane Nugent Cochems, has requested the Dean of the University of Colorado School of Medicine to conduct the competition. The judges appointed by him are Dr. Michael E. DeBakey, Professor and Head of the Department of Surgery, Baylor University College of Medicine and Dr. Sol Sherry, Professor of Medicine, Washington University School of Medicine.

Papers submitted in the competition may not be published until after the winner of the competition has been announced. At that time the winning paper and all others may be published at the discretion of individual authors. It should be noted, however, that those involved in conducting the competition will not assume any responsibility for submitting manuscripts for publication nor for any costs incident thereto. The winning paper, if published, must carry the designation "Awarded the Jane Nugent Cochems Prize."

Questions regarding the competition and all manuscripts should be directed to Dr. Robert J. Glaser, Vice President for Medical Affairs and Dean of the University of Colorado School of Medicine, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 20, Colo.

A seminar on PEDIATRIC CARDIOLOGY, sponsored by the medical staff, will be held at Childrens Memorial Hospital, Omaha, Nebraska, on May 8, 1961. Principal speakers will be C. Walton Lillehei, M.D., Professor of Surgery, University of Minnesota, and James W. DuShane, M.D., Section of Pediatrics, Mayo Foundation, Associate Professor of Pediatrics, University of Minnesota.

A complete program and registration blank may be obtained by writing to Postgraduate Seminar, Childrens Memorial Hospital, Omaha 5, Nebraska.

COURSES FOR PHYSICIANS IN NONSURGICAL METHOD OF REVIVING STOPPED HEARTS. The American Heart Association has announced that it has scheduled 20 half-day courses in nine cities throughout the nation in which physicians will be instructed in a new nonsurgical method of restoring the beat to a stopped heart. The first of these teaching sessions was held on January 5 in New York City for invited physicians from the upper Atlantic region.

Known as "closed chest cardiac resuscitation," the new technique has received wide attention in the medical profession since it was first described some months ago by a team of scientists at Johns Hopkins Hospital (Baltimore). The Johns Hopkins team, which includes Dr. W. B. Kouwenhoven, Dr. James R. Jude and Dr. G. Guy Knickerbocker, has agreed to serve as instructors for the courses sponsored by the Heart Association. In addition, the February issue of the Heart Association monthly publication for physicians, *Modern Concepts of Cardiovascular Disease*, was devoted to an article on this subject by the Johns Hopkins group.

Previous methods of starting up a stopped heart required either administration of an electric shock or opening of the chest in order to massage the heart by hand. In the closed chest technique reliance is placed primarily on controlled intermittent pressure of the hand placed over the patient's breastbone.

When correctly applied this method has been found to be successful in restoring the heartbeat in 70 per cent of cases. Its application by untrained persons is not without hazard, however, and for this reason the professional teaching institutes have been arranged. Physicians invited to attend the first 20 courses will be expected to conduct similar teaching sessions for other doctors in their home communities, the Heart Association said, with a view to disseminating information on the new technique throughout the United States. It is not planned at the present time to teach the method to nonprofessional persons.

Physicians who wish to attend one of these teaching sessions are asked to communicate with their local Heart Association affiliate. In each case separate morning and afternoon courses of 3 hours will be held, with attendance at each limited to 50 physicians. In addition to the opening sessions in New York, courses were scheduled for February 1 in Los Angeles and subsequently in other cities to be announced.

The Annual Convention of the NATIONAL GERIATRICS SOCIETY will be held on May 1-4, 1961, at the St. Francis Hotel, San Francisco, Calif.

For further information write to Ira O. Wallace, President, National Geriatrics Society, 5 Park Towne South, Philadelphia 30, Pa.

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Editorial

Thrombolytic therapy

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The successful development of a practical form of therapy designed for the rapid dissolution of thrombi recently formed in the vascular bed would represent a major therapeutic advance. No one would welcome more the virtues of such a therapeutic advance than the cardiologist who daily observes the ravages of the thrombotic complications of atheromatous disease of the coronary vessels. The recent introduction into clinical medicine of thrombolytic preparations for the treatment of peripheral and pulmonary thromboemboli suggests that clot-dissolving agents may soon be recommended for the treatment of acute coronary thrombosis and myocardial infarction. If so, then it behooves us to examine carefully the current status of thrombolytic therapy.

Thrombolytic therapy is based on the principle that clots can be dissolved enzymatically in vivo provided that the circulating plasma is endowed with an increased clot-dissolving or thrombolytic activity for adequate periods of time. Evidence supporting this principle has been obtained repeatedly both from in vitro and in vivo studies. In animals, unequivocal evidence has been obtained that systemic thrombolytic states of the requisite degree successfully mediate the dissolution of experimentally induced thrombi,[1] and similar observations now have been made in man. Thus, the initial objective in thrombolytic therapy is to impart and sustain in the circulating plasma a powerful clot-lysing ability. Thrombolytic agents represent the means by which such enhanced thrombolytic or clot-dissolving activity can be induced, controlled, and maintained in the patient.

Unfortunately, considerable controversy exists among investigators as to whether the desired therapeutic thrombolytic state can be more readily and more safely achieved by substances, such as streptokinase or urokinase, which activate the naturally occurring but normally quiescent fibrinolytic enzyme system, or by the direct use of plasmin, the proteolytic enzyme which ultimately is involved in the natural resolution of fibrin. The biochemical and pharmacologic basis for this controversy is more complex than the simple choice of agents which in vitro may produce similar effects; the interested reader should consult recent articles which deal with this aspect of the problem.[2] Regardless of this fundamental controversy, the principle concerning the induction and maintenance of a measurable regulated thrombolytic state in the circulating plasma is in no way circumvented by the nature

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of the agent used for thrombolytic therapy.

The two thrombolytic preparations available commercially, Actase and Thrombolysin, though both designated by their manufacturers as human fibrinolysin (plasmin) are on analysis mixtures of streptokinase (a bacterial activator derived from hemolytic streptococci) and plasmin (the proteolytic enzyme derived from human plasma). However, the thrombolytic activity they induce in plasma (in vivo and in vitro) can be traced to their streptokinase content.

Different problems are posed by each of the two preparations. Actase contains relatively small amounts of both streptokinase and plasmin. In vitro evidence suggests that the infusion of 1-2 vials of this preparation into man, as advised, could hardly be expected to exert any detectable effects, since the circulating plasma contains sufficient antiplasmin and antistreptokinase (all adult plasma contains large amounts of antiplasmin and, consequent to previous streptococcal infection, significant but variable amounts of antistreptokinase) to inactivate rapidly the recommended dose of this agent. The prediction that this agent in the recommended doses would fail to raise plasma thrombolytic activity in vivo has been confirmed by direct experimental trials in man.[illegible]

In contrast, Thrombolysin contains considerably more streptokinase and plasmin per vial. Though the antiplasmin activity of the circulating plasma is still readily sufficient to inactivate all the plasmin present, there is sufficient streptokinase in this preparation, when used in the recommended dose of 4 or more vials per day, to induce an active thrombolytic state in some patients comparable to that which would have been induced by streptokinase alone. Since Thrombolysin is best viewed as a streptokinase preparation containing added plasmin, its proper use for instituting a reproducible thrombolytic state should be governed by the same considerations which apply for streptokinase alone, where patient dosage (based on a dose prediction test) must be *individualized* depending upon the amount of circulating antistreptokinase.[illegible] The fixed or standard dosage schedule currently recommended for Thrombolysin makes it impossible to insure that the patient will develop an active thrombolytic state, and the lack of laboratory controls makes it impossible to determine what type of thrombolytic state is being evaluated therapeutically. For this reason it is essential that the haphazard nature of the enzymatic state induced in patients with this agent be replaced by a well regulated one before studies are undertaken to determine its clinical efficacy in the treatment of disease.

Serious problems also have arisen concerning the standardization of the commercially available streptokinase-plasmin mixtures. These mixtures are currently standardized in terms of arbitrary fibrinolytic units, and each manufacturer has his own. The need for appropriate standardization is emphasized by the fact that a vial of Actase of 50,000 fibrinolytic units contains less than one quarter the streptokinase unitage and one twentieth the plasmin unitage of a vial of Thrombolysin, also described as containing 50,000 fibrinolytic units.[1] Furthermore, the fibrinolytic assay employed fails to distinguish between the relative concentration of the two components, each of which is handled entirely differently in vivo. Intelligent use of these preparations requires that the content of their individual components be known.

Some of the other as yet unsolved problems of thrombolytic therapy can be illustrated by a consideration of the application of this type of treatment to coronary heart disease. Progress in this development has been recently reviewed[illegible] and the magnitude of the problem as regards clinical evaluation discussed. However, any trial with thrombolytic therapy, if it is to be meaningful, must evaluate a controlled thrombolytic state, not just the administration of a particular agent with a variable response in patients. Thus decisions must be made concerning the nature and duration of the thrombolytic state to be evaluated and the laboratory controls to be used in guiding therapy. These laboratory controls, to be most practical, must be simple ones, a matter of particular importance if the results indicate that the therapy may be recommended for general clinical use. With the streptokinase system (which is applicable to the currently available commercial prepara-

tions) simple tests are available for predicting dosage and the induced (occasionally hazardous) coagulation disorder *may* be monitored by serial antithrombin times. Still needed is a simple reliable quick test for adequately following plasma thrombolytic activity.

Finally, it has been our conviction that thrombolytic agents should not be used in extensive clinical trials until they are virtually free of pyrogenic activity. Although the incidence of such reactions has in general steadily decreased with increasing purity of the preparations, the problem of eliminating or preventing this undesirable feature has not been solved completely. Febrile reactions prevent the maintenance of adequate thrombolytic therapy and in critically ill patients may provoke a fatal outcome. In acute myocardial infarction where thrombolytic therapy under optimal circumstances only can hope to benefit a moderate number of patients, i.e., those with underlying thrombi and salvable myocardium, the over-all beneficial effects could be virtually eliminated by a relatively small but significant incidence of severe pyrogenic reactions. Though some investigators have found it expedient to limit thrombolytic therapy to a 4 hour period so as to minimize the problem of pyrogenicity, experimental observations suggest that such expediency may well eliminate the major portion of the therapeutic benefit since under controlled conditions long periods of treatment are often necessary to effect and sustain the complete dissolution of a thrombus.[7] Because pyrogenic reactions jeopardize both the therapy and the patient, it would seem wisest to concentrate on eliminating the cause of such reactions.

The current emphasis on practical trials with thrombolytic agents rather than the *further development of scientific principles* is a matter of considerable concern. Obviously there is a compelling need for practical trial once the science and pharmacology of a desired thrombolytic state induced by a particular agent is sufficiently established, but the encouragement of practical trial in lieu of the establishment of sound principles is not sensible. The argument raised in favor of practical trials before the establishment of therapeutic principles is that the effect in patients is paramount; therefore, if an effect is apparent, other considerations are relatively of little importance. Such a view may have virtue in the treatment of diseases in which the natural course is well defined and predictable, such as certain malignant or infectious diseases. However, the application of scientific method to the evaluation of an agent in the treatment of diseases with extremely variable symptomatic morbidity and mortality patterns, such as the thromboembolic disorders, is the most difficult in the entire area of clinical investigation, and an empirical clinical evaluation in trials based on inadequately controlled or limited studies defies critical analysis.

One cannot expect resolution of the confusion surrounding the current state of thrombolytic therapy until such basic problems as the choice of agents, simple laboratory guides for instituting and controlling therapy, proper standardization of agents, elimination of pyrogenic contaminants, etc., are solved sufficiently to allow for the establishment of sound pharmacologic principles in the development of thrombolytic therapy. The inherent potential with this form of therapy is so great and preliminary human observations sufficiently promising that major encouragement should be directed toward the solution of these fundamental problems both by laboratory investigation and carefully planned trials which correlate clinical and laboratory measurements. Conversely, we must recognize that we are insufficiently advanced in the development of scientific principles to encourage clinical trials under any except clinical investigative circumstances. Only with the establishment of a firm foundation will this new and exciting field of therapeutics develop soundly at the clinical level.

REFERENCES

1. Sherry, S., and Fletcher, A. P.: Proteolytic enzymes: therapeutic evaluation, Clin. Pharmacol. & Therap. 1: 70, 1960.
2. Johnson, A. J., and Tillett, W. S.: The lysis in rabbits of intravascular blood clots by the streptococcal fibrinolytic system (streptokinase), J. Exper. Med. 95: 449, 19[illegible]
3. Sherry, S., Titchener, A., Gottesman, L., Wasserman, P., and Troll, W.: The enzymatic dissolution of experimental arterial thrombi in the dog by trypsin, chymotrypsin and plasminogen activators, J. Clin. Invest. 33: 1303, 19[illegible]

4. Johnson A J and McCarty W R The lysis of artificially induced intravascular clots in man by intravenous infusions of streptokinase J Clin Invest 38 1627 1959
5. Alkjaersig N Fletcher A P and Sherry S The mechanism of clot dissolution by plasmin J Clin Invest 38 1086 1959
6. Ambrus C M and Markus G Plasmin antiplasmin complex as a reservoir of fibrinolytic enzyme Am J Physiol 199 491 1960
7. Roberts H R and Geratz J D editors Proceedings of the conference on thrombolytic agents Chicago 1960 Chapel Hill University of North Carolina 1960
8. Brinkhous K M and Roberts H R Thrombolysis and thrombolytic agents J A M A [illegible] 1961
9. Sherry S Fletcher A P and Alkjaersig N Fibrinolysis and fibrinolytic activity in man Physiol Rev 39 343 1959
10. Fletcher A P Alkjaersig N Sawyer W D and Sherry S Evaluation of human fibrinolysin (Actase) Lack of fibrinolytic activity after intravenous administration in man J A M A 172 912 1960
11. Fletcher A P Alkjaersig N and Sherry S The assay of thrombolytic ("fibrinolytic") mixtures intended for therapeutic use J Lab & Clin Med 57 1961 (In press)
12. Watt D L and MacMillan R L Evaluation of intravenous human fibrinolysin as a treatment for recent intravascular thrombosis Canad M A J 83 1436 1960
13. Fletcher A P Alkjaersig N and Sherry S The maintenance of a sustained thrombolytic state in man I Induction and effects J Clin Invest 38 1096 1959
14. Nydick I Ruegsegger P Abarquez R Clifton E E and LaDue J S The effect of fibrinolytic agents on myocardial infarction Prog Cardiovas Dis 3 13 1960
15. Fletcher A P and Sherry S Thrombolytic (fibrinolytic) therapy for coronary heart disease Circulation 22 619 1960
16. Nydick I Ruegsegger P Bouvier C Hutter R V Abarquez R Clifton E E and LaDue J S Salvage of heart muscle by fibrinolytic therapy after experimental coronary occlusion Am Heart J 61 93 1961
17. Fletcher A P Sherry S Alkjaersig N Smyrniotis F E and Jick S The maintenance of a sustained thrombolytic state in man II Clinical observations on patients with myocardial infarction and other thromboembolic disorders J Clin Invest 38 1111 1959

Clinical communications

Endocardial fibroelastosis

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The term *endocardial fibroelastosis* was introduced by Weinberg and Himelfarb[1] in 1943 to describe a cardiac condition of obscure etiology in infancy in which the most striking feature was diffuse left ventricular endocardial thickening. As a term it has proved to be the most widely used among the many which have been applied to similar cases.

It has since been the practice to include under this term all kinds of endocardial thickening in infancy and early childhood and, in addition, to refer to morphologically similar cases seen in European and North American adolescents and adults as *endocardial fibroelastosis* of these age groups.[2] The assumption is often made that these adult cases are in some way connected with the infantile condition, but this is open to question. Moreover, the correctness of the term *endocardial fibroelastosis* even as it is applied in infancy is also questionable since it is descriptive only of the endocardial condition and does not indicate any other cardiac anomaly which may and often does accompany the endocardial thickening. Further and more important, it implies that the endocardial lesion is the primary one, whereas there is a great deal of evidence to the contrary.

The pattern of endocardial fibroelastosis

The condition is characterized by a diffuse fibroelastic thickening of the endocardium (Fig. 1) which in the majority of cases is confined to the chambers on the left side, particularly the left ventricle. The right ventricular endocardium may in a few cases be thickened, but the degree and severity of the change is not comparable with that seen on the left. In about half of the reported cases some other cardiac condition was also found, the most common being aortic stenosis. The condition is found in early infancy, and as a rule death occurs between the age of 3 and 12 months, and it may be sudden. There is no significant sex variation; it is found in both white and Negro children, and there are several reports of it occurring in twins and siblings.[4]

Until recently, all hearts which showed diffuse endocardial thickening have been considered as a single group, but when a large number of cases are reviewed they fall naturally into two main categories: (1) those cases in which the endocardial thickening is accompanied by some other gross cardiac anomaly and (2) those in which the mural endocardial thickening appears to be the only lesion of significance. In the first category, the most common concomitant conditions by far are aortic and mitral stenosis, particularly the former. Others may occur, but none with any frequency—for example, premature closure of the foramen ovale,[7] an adult type of coarctation of the aorta, ventricular septal defects, and the triad of aortic atresia, hypoplasia of the aorta, and rudimentary left ventricle.[8] Often included with these is the syndrome of anomalous left coronary artery, but this should be

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Fig. 1. The diffuse fibroelastic endocardial thickening from a case of endocardial fibroelastosis without valvular disease. (Weigert's elastica. ×90.)

regarded as a separate condition, although diffuse left ventricular endocardial thickening is present in all examples.

Cases in the second category are perhaps less common but of more interest. Here no other lesion apart from the endocardial thickening is apparent and this circumstance has in the past caused confusion since it was often argued that if the mural endocardial lesion could occur alone, the valvular lesions seen in the other group were not essential and due only to an extension of the mural process. Thus the possibility that two groups were present, linked only by endocardial thickening, was seldom considered.

The etiology of endocardial fibroelastosis

In the past a variety of theories have been put forward to account for the endocardial thickening with or without valvular disease. The earliest theory was that the lesions were the result of a fetal endocarditis, but it has been shown that this assumption had no evidence to support it. Others[11, 12] believed that the lesion was a congenital cardiac anomaly arising probably from the overgrowth of connective tissue to involve both valves and mural endocardium. The source of this has never been determined and the embryologic arguments advanced are unconvincing, particularly when an explanation of the group of cases without valvular disease is attempted.

Johnson proposed that in all cases of endocardial fibroelastosis the cause was anoxia of the endocardium. This he suggested was due to a deficient coronary blood supply which resulted from either aortic stenosis or an anomalous left coronary artery, or defects in the perforation or closure of the foramen ovale. This hypothesis has received some support,[1] but it has several defects. First, it seems particularly difficult to render the endocardium anoxic since it receives its main supply of blood directly from the ventricle. Secondly, there is no evidence that anoxia per se produces endocardial thickening, and third, the hypothesis does not explain the group of cases with no demonstrable defects other than left ventricular endocardial thickening.

The anoxic theory has been challenged,[8] and it has been proposed that conditions predisposing to increased intracardiac pressure and dilatation are present in all cases and that these mechanical factors produce a reactive diffuse endocardial thickening. This is in accordance with the views of earlier investigators.[13]

Recently, too, the distinction between the two groups already referred to has been made[5] and the cause in this group without valvular disease has been considered to be almost by exclusion some defect in cardiac muscle which is not morphologically obvious. Evidence is now forthcoming that this group may have a congenital defect of cardiac muscle termed *myocardial hyperplasia*.[22] This state is defined as one in which the cardiac fibrils remain at their immediately prenatal size and do not increase in size, as is seen in hearts with valvular disease and also in normal growth. It has also been suggested that in this group of cases there is an inborn enzymatic defect which acts on the cardiac muscle.[23] The connection between hyperplasia and this enzymatic defect is not yet clear.

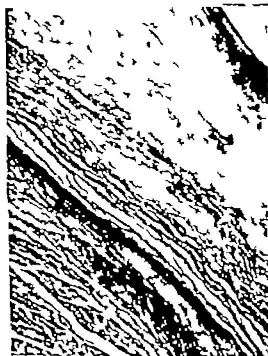


FIG. 2 Endomyocardial fibrosis (Uganda). The superficial area of the endocardium are composed of mural thrombus and hyaline material. Hematoxylin and eosin ×130

With regard to the connection between endocardial thickening and increased intracardiac pressure and dilatation, there are several adult states in which this sequence appears to be present—for example in the left auricle in association with mitral stenosis[44] as a sequelae of left ventricular dilatation for a variety of reasons, and a similar type of endocardial thickening is seen in the dilated left ventricle of adolescents who die from pseudo hypertrophic muscular dystrophy

In most examples of diffuse endocardial thickening in infancy circumstances exist which produce either increased intracardiac pressure or dilatation or both—for example aortic stenosis, the massive myocardial fibrosis in anomalous left coronary artery and congenital hyperplasia of cardiac muscle. Thus as far as it goes the hypothesis is satisfactory but discrepancies exist, for example cardiomegaly occurs without endocardial thickening and not all valvular diseases in infancy or for that matter in adults are complicated by diffuse endocardial thickening

The pathogenesis of the endocardial thickening

Little attention has been paid to the processes which thicken the endocardium in cases of endocardial fibroelastosis. Theoretically there are three ways by which the result may be brought about (1) by the deposition and incorporation of mural deposits (2) by an overgrowth of connective tissue and (3) by replacement fibrosis

In the common types of adult endocardial thickening particularly in African endomyocardial fibrosis (Fig 2) in myocardial infarction (Fig 3) and in mural rheumatic endocarditis (Fig 4) the thickening is in some measure due to the deposition and incorporation of mural thrombi and this will eventually lead to fibroelastic thickening of the endocardium similar to that of endocardial fibroelastosis (Fig 5)

If the endocardium in the infant condition is examined with these mural deposits in mind it will be found that they occur with some frequency (Figs 6 and 7) Besides the more obvious recent surface deposits there are other appearances which suggest that similar processes have occurred



FIG 3 Myocardial infarction Organizing mural thrombus overlying an area of myocardial infarction



Fig 4 Rheumatic endocarditis A biopsy specimen showing two small mural deposits being incorporated Hematoxylin and eosin X150

in the past For example quite often the intratrabecular cleft in the left ventricle are filled with loose vascular connective tissue so that they are wholly or partly obliterated and at times material which stains as fibrin can be found in this tissue (Figs 8 and 9) This process aided by the intraventricular pressure tend to flatten and smooth the surface of the left ventricle producing the characteristic gross appearance A further example of surface activity is seen in other areas in which the endocardium has a vascular almost granulation tissue appearance with small tags of fibrin adhering to it (Fig 10) and in addition in many areas the superficial layers are of a spongy loose texture (Fig 11) suggestive of fairly recent formation

It has further been shown[21 ?] that when these surface layers of the endocardium are examined by the electron microscope they are found to contain fibrin which is not apparent in contiguous histologic sections This would seem to indicate that the deposition and incorporation of fibrin are more widespread than the histologic appearances would suggest and therefore more important in the pathogenesis of the thickening than at first seems likely

To most observers however the endocardial thickening has been taken as some type of hyperplasia—either a reaction to anoxia or to increased strain It is true that the endocardium for the most part looks as though the normal tissue elements have been multiplied some tenfold but there is no method by which we can judge the extent or degree of the hyperplasia and it must be borne in mind that a similar type of endocardial thickening can be produced largely by the organization of mural thrombi

Some degree of subendocardial fibrosis and replacement fibrosis of the subjacent myocardium are common features of endocardial fibroelastosis but the severity of these changes vary widely It does seem likely however that they are more conspicuous in hearts with valvular stenosis [?] These processes are not in fact part of the endocardial thickening although it is difficult to separate the layers when fibrosis is extensive and it is likely that for the most part this distinction has not been made



Fig 5 Myocardial infarction Fibroelastic thickening of the endocardium overlying a healed infarct Weigert elastica X100



Fig 6 Endocardial fibroelastosis Recent but organizing thrombotic deposit in the left ventricle Hematoxylin and eosin ×100

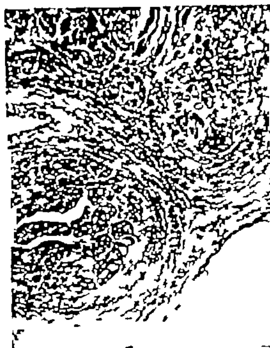


Fig 8 Endocardial fibroelastosis An intratrabecular cleft partly obliterated by vascular connective tissue Hematoxylin and eosin ×110



Fig 7 Endocardial fibroelastosis Small deposits of fibrin in intratrabecular cleft. Hematoxylin and eosin ×180

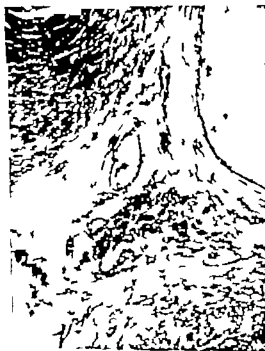


Fig 9 Endocardial fibroelastosis Trabeculae joined by loose vascular connective tissue which contains fibrin Hematoxylin and eosin ×120



Fig. 4. Rheumatic endocardit . A biopsy specimen showing tw small mural depo its bein incorporated. Hematoxyli nd eos . ×130.

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Fig. 5. My ocar l l infarction. Fibroela tic thicken in of the end card um overlying healed infarct. Wei ert lastica. ×100.



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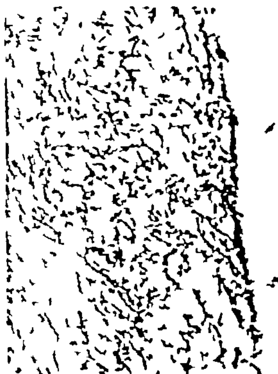


Fig. 10. ... the endocardial surface ... of granulation tissue ... ×180.

Adult and adolescent endocardial thickening

There are numerous reports on endocardial thickening in adults and a lesser number of reports on adolescents in which the etiology is obscure. The tendency has been to label those cases as *endocardial fibroelastosis*; some workers have been inclined to the view that they are surviving examples of infantile endocardial fibroelastosis,[3] whereas others have regarded the endocardial thickening here as a nonspecific reaction to a number of different underlying cardiac conditions. At present the cases are too heterogeneous for any real order to emerge, if order does in fact exist. No connecting factors have been found between these scattered European and North American cases with the more well-defined African type of endocardial thickening known as *endomyocardial fibrosis*[34] on one hand and the infantile endocardial fibroelastosis on the other.

With regard to the connection with the infantile condition there are several points of difference. First, the adult and adolescent cases seldom if ever show the diffuse type of endocardial thickening characteristic of the infantile group; thickening in the adult and adolescent tends to be more patchy. Secondly, the degree of myocardial fibrosis is much greater in the adult and adolescent cases. This latter has been dismissed as an effect of the long-standing endocardial thickening, but the evidence from other types of endocardial thickening suggests that this sequence is dubious and that it is the presence of the myocardial fibrosis which is probably of primary importance. It should be noted also that the adult and adolescent thickening is always much more obviously due to the incorporation of mural thrombi and fibrin deposit than to the infantile type of thickening. Furthermore, the histories of the adult and adolescent cases suggest that the first episode of cardiac failure was of sudden or relatively sudden onset after apparent good health, a history somewhat inconsistent with their having possessed since infancy a progressive variety of infantile endocardial fibroelastosis.



Fig. 11. Endocardial fibroelastosis. The surface layer is spongy in texture and contains little elastic tissue. (Hematoxylin and eosin ×150.)

Conclusions

It seems likely that the condition which at present we call *endocardial fibroelastosis* is a disease of infancy and moreover can be divided into two distinct groups In one group severe independent lesions are present particularly aortic stenosis and these appear to be the factor of primary importance with the diffuse endocardial thickening as one of the effects of the lesion on the related chamber In the second group the mural thickening is not accompanied by other gross cardiac defects but may be related to a congenital hyperplasia of cardiac muscle and may again be only a sequelae to the cardiac dilatation which ensues from this state The term *endocardial fibroelastosis* is not suitable therefore for either group since in neither is the endocardial lesion the primary change

Summary

The etiology and pathogenesis of so called endocardial fibroelastosis is reviewed in the light of recent information It is suggested that the endocardial lesion is secondary to increased intraventricular pressure and dilatation caused by some other cardiac anomaly and that the incorporation of surface deposits of fibrin play a part in the pathogenesis of this endocardial thickening

REFERENCES

1 Weinberg T and Himelfarb A J Endocardial fibroelastosis (so-called fetal endocarditis) A report of 2 cases occurring in siblings Bull Johns Hopkins Hosp 72 299 1943
2 Thomas W A Randall R V Bland E F and Castleman B Endocardial fibroelastosis A factor in heart disease of obscure etiology A study of 20 autopsied cases New England J Med 251 327 1954
3 Auld W H R and Watson H Fibroelastosis of the heart in adolescence Brit Heart J 19 186 19 7
4 Dyson B C and Decker J D Endocardial fibroelastosis in the adult A M A Arch Path 66 190 1958
5 V Bochem F S P Arends A and Schroder E A Endocardial fibroelastosis in adolescents and adults Brit Heart J 2 279 1959
6 Winter S T Moses W S Cohen N J and Naftalin J M Primary endocardial fibroelastosis A M A J D Child 99 529 1960
7 Johnson F R Anoxia as cause of endocardial fibroelastosis in infancy A M A Arch P th 51 57 195
8 Kelly J and Andersen D H Congenital endocardial fibroelastosis II A clinical and pathological investigation of those cases without associated cardiac malformations including report of familial instances Pediatrics 18 539 1956
9 Horley J F Foetal fibroelastosis Brit M J 1 765 1955
10 Gross P Concept of fetal endocarditis A general review with report of an illustrative case Arch P th 31 163 1941
11 Cosgrove G E and Kaump D H Endocardial sclerosis in infants and children Am J Clin Path 16 322 1946
12 Craig J M Congenital endocardial sclerosis Bull Internat A M Mus 30 15 1949
13 Prior J T and Wyatt T C Endocardial fibroelastosis A study of eight cases Am J Path 26 969 1950
14 Collier F C and Rosahn P D Endocardial fibroelastosis Report on tw cases Pediatrics 175 1951
15 Gowing N F C Congenital fibroelastosis of the endocardium J Path & Bact 65 13 1953
16 Kempton J J and Glynn L E Heart failure in infancy with abnormalities of the alves and endocardium Quart J Med (N S) 24 191 1955
17 Levy D and Falk W Endocardial fibroelastosis Acta Med Orient 15 1 1956
18 Black Schaffer B Infantile endocardial fibroelastosis A suggested etiology A M A Arch Path 63 281 1957
19 Loeser A Über kongenitale Aortenstenose und foetale Endocarditis Virchow Arch path Anat 219 309 1915
20 Hertel M P Das Verhalten des Endokards bei parietalen Endokarditis und bei allgemeiner Blutdrucksteigerung Frankfurt Ztschr Path 24 1 1921
21 Boger A Über die Endocard klerosen Beitr path Anat 81 441 1929
22 Black Schaffer B and Turner M E Infantile hyperplastic cardiomegaly Am J Path 34 584 1958
23 Lambert E C and Vlad P Primary endocardial d sease Pediat Clin N Amer 3 1057 1958
24 Ferencz C Johnson A L and Wigglesworth F W Congenital mitral stenosis Circulation 9 161 1954
25 Flynn J E and Mann F D Presence and pathogenesis of endocardial and subendocardial regeneration mitral thrombi and thrombosis of the Thebesian eins in cardiac failure from causes other than myocardial infarction Am Heart J 31 757 1946
26 Levin S Baens G S and Weinberg T The heart in pseudohypertrophic muscular dystrophy J Pediat 55 460 1959
27 DeMuth G R and Landing P H The occurrence and possible significance of generalized scular disease in idiopathic cardiac hypertrophy Am Heart J 50 643 1955
28 Still W J S and Boult E H Pathogenesis of endocardial fibroelastosis Lancet I 117 1956
29 Still W J S and Boult E H The electron microscopy of endocardial fibroelastosis Arch Dis Childhood 32 298 1957
30 Davies J N P and Ball J D The pathology of endomyocardial fibrosis in Uganda Brit Heart J 17 337 1955

Perinatal changes in the pulmonary vascular bed with stenosis and atresia of the pulmonic valve

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Certain congenital cardiac anomalies lead to extensive anatomic and physiologic alteration in the pulmonary arterial bed. These have usually been noted when the lesser circulation has been subjected to increased pressure and volume of blood flow.[1] The possibility exists that major changes may also develop in the pulmonary arteries when pressures and flow are abnormally reduced. Such a reduction may occur when the pulmonic valve is narrowed or closed. In the present report, congenital pulmonic stenosis and atresia are shown to lead to an abnormal fetal development of the pulmonary arterial bed which is often continued after birth. We are unaware of any previous report of such an abnormal development.

Subjects

Fifteen infants with pulmonic stenosis who died during the perinatal period were studied. Two were stillborn; the rest varied in age from 24 hours to 16 weeks. Stenosis was severe in all cases. The ductus arteriosus was anatomically closed in all who were over 3 weeks of age. In one infant (1 day old) the ductus arteriosus was apparently closed at birth. In most instances the pulmonary artery was described as being hypoplastic. Seven of the infants had tetralogy of Fallot. Over-all cardiac enlargement was described in many instances. Both in infants with tetralogy and in infants with isolated pulmonic stenosis the right atria were noted to be dilated. In 10 of these infants the right ventricle was described as being abnormally thick walled.

In all of the infants cyanosis was noted at or soon after birth. Early respiratory distress was noted in about one half. Five were reported to be weak and lethargic in the days after birth. Of those who survived for a time, most had feeding problems and gained weight poorly. Five were found to have a cardiac systolic murmur. Two who survived for several weeks developed polycythemia. Thoracic x-ray films revealed a reduced pulmonary vascular pattern as well as an enlarged heart in 3 infants. Peripheral edema and congestive hepatic enlargement were noted in 4.

Also studied were 21 infants with pulmonic valvular atresia who were stillborn or lived less than 16 weeks after birth. Hypoplasia of the pulmonary arteries was described in 10, and 5 had only atretic cords where the pulmonary artery is usually found. In 6 infants the only blood supply for the lungs was through the bronchial

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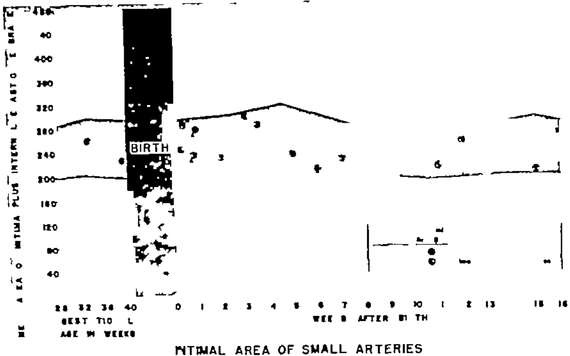


Fig 1 The mean areas of intima combined with internal elastic membrane for small arteries from patients with pulmonic valvular atresia and stenosis The areas in which normal values are found are lightly shaded Normal values have been published previously

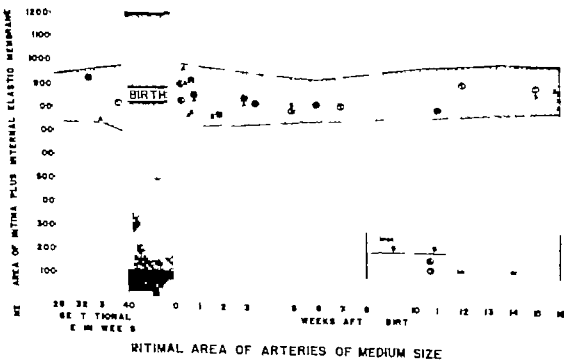


Fig 2 Same as Fig 1 except that values are for medium sized arteries

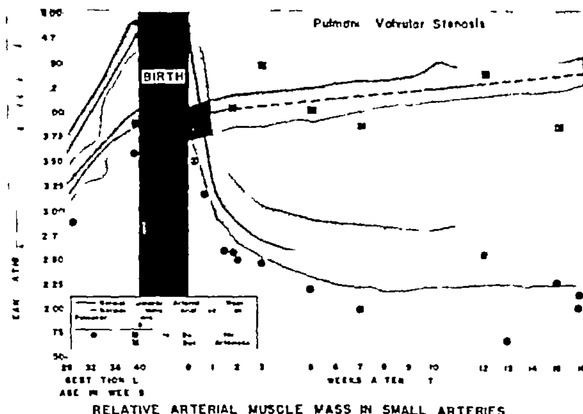


Fig. 3. A ratio reflecting arterial muscle mass for small arteries from patients with pulmonic valvular stenosis. The areas in which normal values are found are lightly shaded. These normal values have been published previously.

arterial system. In the other 15 infants the blood reached the pulmonary circuit through a patent ductus arteriosus. In 3 of these latter cases the ductus was abnormally patent, the infant being more than 3 weeks of age. None of the infants had transposition of the great vessels. One infant (age 23 days) had biatrium triloculare. Some type of interatrial septal defect permitting right-to-left interatrial shunt was found in all cases.

The clinical histories of the infants with pulmonic valvular atresia were similar to those of patients with severe pulmonic stenosis. Liveborn infants were noted to be cyanotic at an early stage, and 3 who survived for more than a month became polycythemic. Weakness, lethargy, and poor feeding were described in 8. A systolic precordial murmur was detected at some time before death in all but 5 of the liveborn infants. X-ray evidence of cardiac enlargement and a reduction of the pulmonary vascular bed were also described in 5 infants. Progressive congestive hepatic enlargement was common before death.

Methods

Previously described methods were used to measure arterial changes in both circulations. In each case multiple blocks of pulmonary tissue selected at random were sectioned at 6 microns and stained with Verhoeff and van Gieson stains. Similar sections were prepared from one or more blocks of pancreas in about one half of the cases. With the aid of a camera lucida and a planimeter, the relative cross-sectional areas of lumen, intima, and media of small muscular arteries and arterioles were determined. In each vessel the internal elastic membrane was arbitrarily included as part of the intima. Sections from cases under study and sections from controls were thoroughly mixed and examined in a random manner to avoid bias.

Results

Initially the mean area of intima combined with internal elastic membrane for vessels in each case was charted against the stage of development (Figs. 1 and 2). These were compared with previously published values for normal controls. The values proved to be relatively similar and constant throughout the period of study for both normal controls and for patients with pulmonic stenosis and atresia. Therefore the relative areas of these structures were selected as a convenient reference base line to which the arterial medial mass could be compared. As in the previous study, a numerical expression

$$\frac{\text{area arterial or arteriolar media}}{\text{area intima} + \text{internal elastic membrane}}$$

was adopted as a relative measure of arterial muscle mass. In each case this value was determined for 15 to 30 arterioles and small arteries in the pulmonary circulation with luminal diameters between 5 and 30 microns. A similar number of arteries with luminal *diameters* between 30 and 50 microns were also measured. *In those cases* in which tissue was available, measurements were also recorded for the systemic circulation. These two categories of small vessels were selected because they presumably make a major contribution to vascular resistance.

In patients with pulmonic stenosis, vessels of the systemic arterial bed were found to be normal. The arteries and arterioles were well developed and examination of the ratio

$$\frac{\text{area media}}{\text{area intima} + \text{internal elastic membrane}}$$

showed that the medial muscle coat of these vessels was normal in area (Figs. 3 and 4). Values for normal controls have been published previously. In contrast, abnormalities in medial mass were present in the pulmonary arterial bed. Both before and after birth, ratios were about 20 per

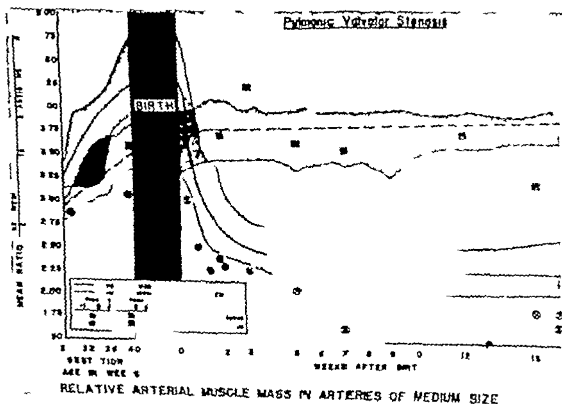


Fig. 4. A ratio reflecting arterial muscle mass for medium sized arteries from patients with pulmonic valvular stenosis. Normal values are found within the lightly shaded areas.

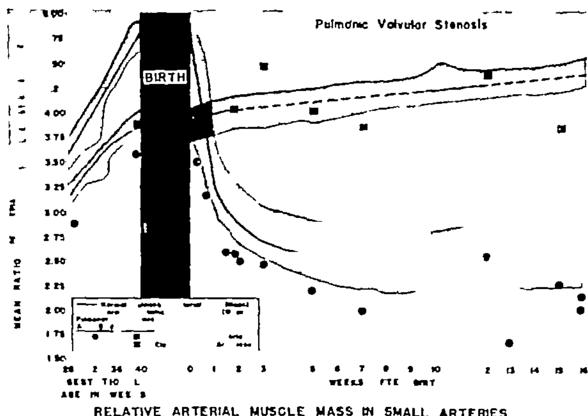


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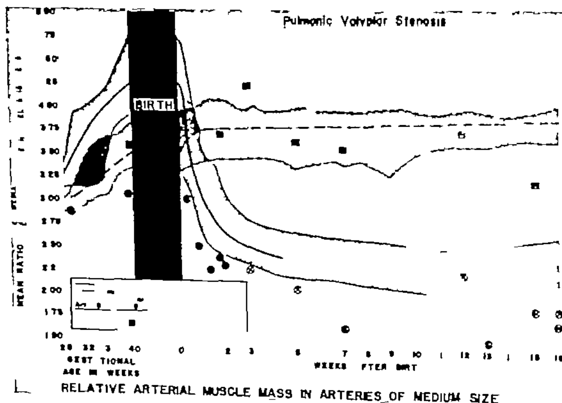


Fig 4 A ratio reflecting arterial muscle mass for medium sized arteries from patients with pulmonic valvular stenosis Normal values are found within the lightly shaded areas

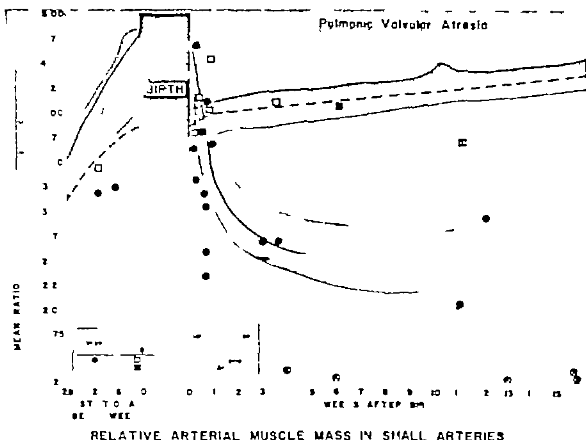


Fig. A ratio reflecting arterial muscle mass for small arteries from patients with pulmonic valvular atresia. The areas in which normal values are found are lightly shaded.

cent smaller than those found in control cases (Figs. 3 and 4). This diminution in smooth muscle was found in arteries and arterioles of all sizes. Abnormalities of the intima or elastic membrane were absent and the pulmonary veins and bronchial vessels were structurally normal.

Many of the findings in patients with pulmonic atresia were similar. The muscular coat about the systemic arterial bed developed normally both before and after birth (Figs. 5 and 6). In contrast, the values for muscle about the pulmonary arterial bed before birth were considerably lower than the control values (Figs. 5 and 6). Of the 10 liveborn infants who survived for less than 1 week, 6 had values below those found in any of the control cases. None had values above those found in the control cases.

In those infants with atresia who survived for 3 weeks or longer, changes in the pulmonary arterial muscle mass seemed to be related to the patency of the ductus arteriosus. In the 6 infants in whom the ductus was closed, the muscle mass was much reduced, being only about 50 per cent of control values. In the group of 3 in whom the ductus remained patent, the muscle mass was not reduced but remained at the level found in other infants with atresia at birth (Figs. 5 and 6). Abnormalities of the arterial intima and elastic membrane were absent in the entire group.

Discussion

The current study demonstrates that smooth muscle in the pulmonary arterial bed develops abnormally in some infants with pulmonic stenosis and atresia, both before and after birth. In a group of stillborn infants this muscle mass was abnormally reduced. In fact, this mass was less than that found about comparable systemic arteries, a reversal of the normal pattern.[2] If arterial muscle mass is a reflec

tion of intra arterial pressure in such cases fetal pressures in the greater circulation may have been above those in the lesser circuit Such pressures might have permitted a left to-right shunt through the ductus arteriosus a reversal of the normal direction of flow This postulate obviously needs clinical confirmation

After birth evolution of the pulmonary arterial muscle mass could be correlated with the state of the ductus arteriosus In patients with pulmonic atresia and a closed ductus arteriosus the relative pulmonary arterial muscle mass was at very low levels In such cases the very low pressures in the lesser circulation after birth probably permitted a relative rapid reduction in the pulmonary arterial muscle mass When the ductus closed normally in cases of pulmonic stenosis the relative muscle mass decreased at a normal rate even though it was already at a low level at birth The resultant subnormal level of this muscle mass throughout the neonatal period probably reflected the low pulmonary arterial pressures which exist in such cases[4] In contrast when the ductus remained patent (in cases of pulmonic atresia) the muscle did not decrease but rather maintained itself at the birth level throughout the period of study This was no doubt related to the fact that the lesser circulation was subjected to high systemic pressures Such high pulmonary arterial pressures have been reported in cases with pulmonic stenosis and a patent ductus[4]

In contrast to these findings Dammann and Ferencz[3] have reported that the postnatal pulmonary arterial muscle mass is normal in patients with pulmonic stenosis and atresia Several factors may explain this apparent discrepancy In contrast to their conclusions in 4 of their youngest patients their data show that the relative pulmonary arterial muscle mass was at less than normal levels Also pertinent is the fact that most of their patients were older than were those in the current study If higher pulmonary arterial pressures and blood flow made this longer survival pos

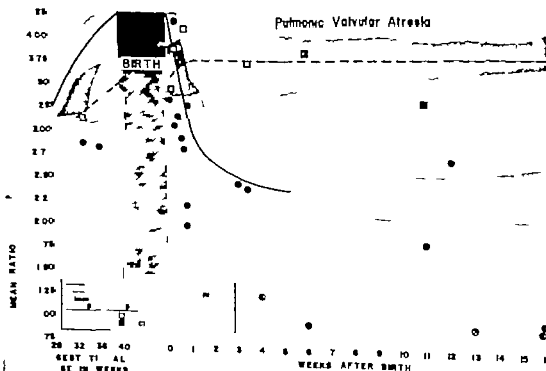


Fig 4 A ratio reflecting arterial muscle mass for medium sized arteries from patients with pulmonic valvular atresia Normal values are found w... ntly shaded area

sible a more nearly normal pulmonary arterial muscle mass would be expected In our cases cyanosis suggested that pressure and flow were very low Lastly Dammann and Ferencz s data may have been subjected to distortion by arterial dilatation or contraction This is inherent in a method which compares thickness of the arterial wall to diameter of the lumen of the artery The method used to measure arterial muscle mass in the current study was probably not influenced by such dilatation and contraction In a previous experimental study it was shown that dilatation of pulmonary arteries had no influence on the ratio used to measure arterial mass in the current study

Summary

The perinatal development of muscle in the pulmonary arteries is influenced by reductions in pressure and flow through these vessels Before birth there is a moderate reduction in the pulmonary arterial muscle mass in cases of both pulmonic stenosis and pulmonic atresia This reduction continues after birth in many cases of pulmonic stenosis In cases of pulmonic atresia in which the ductus arteriosus is closed the pulmonary arterial muscle mass is markedly decreased In cases in which the ductus remains patent the muscle mass does not decrease but is maintained The implications of these findings are discussed

I am indebted to Dr Dorothy Anderson and Dr William Blanc Babies Hospital New York City for case material and valuable suggestion Case material was also kindly supplied by Dr J Lowell Orbison Strong Memorial Hospital Rochester N Y and by Dr John N Abbott Genesee Hospital Rochester N Y

REFERENCES

1 Edwards J F Functional pathology of the pulmonary vascular tree in congenital cardiac disease Circulation 15 164 1957
2 Naeye R L Arterial changes in greater and lesser circulations during the perinatal period A M A Arch Path (In press)
3 Silverman B K Nadas A S Whittenborg M H Goodale W T and Gross R F Pulmonic stenosis with intact ventricular septum correlation of clinical and physiologic data with review of operative results Am J Med 20:53 1956
4 Heiner D C and Nadas A S Patent ductus arteriosus in association with pulmonic stenosis report of six cases with additional noncardiac congenital anomalies Circulation 1 :23 1958
5 Dammann J F Jr and Ferencz C The significance of the pulmonary vascular bed in congenital heart disease I Normal lungs II Malformations of the heart in which there is pulmonary stenosis Am Heart J 52 7 1956

Pathology of the conduction system in acquired heart disease

Complete right bundle branch block

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The anatomic substrate of the electrocardiographic abnormality complete right bundle branch block in acquired heart disease has been a subject of discussion for many years. The literature on this subject has been reviewed by Lenegre[1] and Lev. According to Lenegre, significant lesions in the right bundle branch are found in this electrocardiographic abnormality.

The present work is part of a long term project wherein the purpose is to ascertain the anatomic substrate of disturbances in conduction in general. Previous work dealt *with severe atrioventricular block* and masquerading bundle branch block. The present study was made on 8 cases of coronary disease and 1 of chronic myocarditis with abscesses shortly before death in all of these patients the electrocardiograms showed a pattern of complete right bundle branch block.

Materials and methods

All electrocardiograms were obtained with the Sanborn Viso Cardiette and included the standard and augmented unipolar limb leads and 7 precordial leads (Leads V_{3R} and V_1 to V_6). The diagnosis of a complete right bundle branch block was based on a QRS prolongation to 0.12 second or more and the presence of a slurred or notched R wave or rSR' complex in the right precordial leads. Right ventricular hypertrophy was diagnosed when in the latter leads the QRS was entirely upright (R or rR') or in the presence of an S wave the R measured 10 mm. or more. The presence of left ventricular hypertrophy was assumed when the left sided precordial

Table I. Technical details

	Case		Number of sections
1	(A 55)	R G	986
2	(A 87 56)	S S	961
3	(A– 5 56)	P G	936
4	(A 125–55)	H R	1 04
5	(A 109 55)	M K	1 73
6	(A– 41 55)	H M	918
	(A 1 5–55)	S L	864
8	(A– 95–55)	M O	861
9	(A 182 5)	G S	1 113

From the C[illegible] Diseases Research and Training Center, Michael Reese Institute of Medical Research, the Department of Pathology, Northwestern University Medical School, Chicago, Ill., the Cardiovascular Division of the Department of Medicine, Mount Sinai Hospital, Miami Beach, Fla., and the Cardiovascular Research Department, Michael Reese Hospital and Medical Center, Chicago, Ill.

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Table II Anatomic findings in nine cases of complete RBBB

RBB	Case 1		Case 2		Case 3		Case 4	
								c
S-A node	–	+	–	–	+	–	–	–
Approaches to S-A node	–	+	+	+	4+	–	–	3+
Right atrium	–	–	2+	–	3+	–	–	3+
Left atrium	–	–	2+	–	+	–	–	+
Approaches to A-V node	–	–	+	–	+	–	–	–
A-V node	–	+	–	–	–	–	–	–
A-V bundle penetrating	–	–	–	–	–	–	+	+
A-V bundle branching	–	+	+	+	–	–	2+	+
RBB	+	3+	3+	3+	3+	2+	+	3+
LBB	–	–	3+	+	3+	–	3+	–
Left ventricle anterior	–	3+	2+	+	+	–	–	3+
Left ventricle posterior	–	2+	2+	2+	+	–	–	2 3+
Right ventricle anterior	–	–	+	–	+	–	–	1 +
Right ventricle posterior	–	–	+	–	+	–	–	2 3+
Atrial septum	–	–	+	–	–	–	–	+
Ventricular septum anterior	–	+	2+	+	+	–	+	2+
Ventricular septum posterior	+	3+	2+	+	+	–	2+	2+
LVH	2+		+		+		3+	
RVH	+		2+		+		2+	
Ramus ostii cavae superioris	–		–		–		4+	
Ramus septi fibrosi	+		–		–		2+	
Arteries and arterioles of septum	2+		4+		+		–	

*Acute pathologic change
†Subacute and chronic pathologic change

Table III Correlation of anatomic and electrocardiographic data with regard to right sided or

	Anatomy										
Case	Hypertrophy		Infarction or fibrosis				Bundle branch lesion				QRS duration
							Right		Left		
	Right	Left	R	L A	L P	Septal	Old	Recent	Old	Recent	
1	+	2+	–	3+	2+	2+	3+	2+	–	–	0.12
2	2+	+	+	2+	2+	+	3+	3+	+	3+	0.12
3	+	+		–	(Myocarditis)	–	2+	3+	–	3+	0.12
4	2+	3+	2+	3+	3+	3+	3+	2+	–	3+	0.12
5	3+	4+	+	2+	2+	2+	4+	2+	+	3+	0.14
6	2+	+	2+	+	+	+	4+	–	–	–	0.14
7	–	–	–	+	+	+	–	2+	–	+	0.14
8	4+	4+	+	3+	+	3+	+	3+	–	3+	0.16
9	4+	4+	2+	4+	3+	+	2+	3+	+	3+	0.1 → 0.16

Table II —(Cont'd)

RBB	Case 5		Case 6		Case 7		Case 8		Case 9	
			a				a			
S A node	+	−	−	−	−	−	−	−	2+	−
Approaches to S-A node	±	+	−	+	±	−	±	±	2+	2+
Right atrium	±	1 2+	−	+	±	−	+	−	4+	4+
Left atrium	−	−	−	+	−	−	3+	−	2+	−
Approaches to A V node	±	+	−	+	−	−	−	−	+	−
A V node	±	±	−	±	+	−	−	−	−	−
A V bundle penetrating	±	−	−	±	−	−	−	−	−	−
A V bundle branching	±	+	−	±	−	+	−	−	2+	2+
RBB	2+	4+	±	4+	2+	±	3+	+	3+	2+
LBB	2 3+	+	±	−	+	±	3+	−	3+	+
Left ventricle anterior	±	2 3+	+	±	+	+	3+	−	4+	4+
Left ventricle posterior	+	3+	+	+	+	+	+	−	3+	3+
Right ventricle anterior	−	+	+	2+	+	+	+	±	3+	+
Right ventricle posterior	−	2+	+	2+	+	−	+	±	2+	3+
Atrial septum	−	+	−	+	−	−	2+	−	3+	−
Ventricular septum anterior	2+	2 3+	−	+	2+	2+	3+	−	4+	4+
Ventricular septum posterior	2+	2 3+	±	+	2+	+	4+	2+	4+	4+
LVH	4+		+		±		4+		3+	
RVH	3+		2+		±		4+		4+	
Ramus cristae supraventricularis	−		−		−		−		3+	
Ramus septi fibrosi	4+		−		2+		+		3+	
Arteries and arterioles of septum	−		−		3+		4+		2+	

A was pathol cha ge
Subacute and chron patholog change

left sided ventricular hypertrophy infarction and bundle branch lesions

QRS configuration in V	Electrocardiogram						Correlation of	
	Evidence of							
	Hypertrophy		Infarction			Left sided conduction defect	Hypertrophy	BB lesions
	Right	Left	Anterior	Posterior	Lateral			
QR		−	+	?	−	−	Partial	Excellent
Notched R	+	−	?	?	?	−	Good	Partial
			(Subendocardial injury)					
rSR	−	+	−	−	−	−	Partial	Excellent
Notched R	+	−	Injury	−	−	−	Partial	Partial
R	+	−	+	+	+	±	Partial	Excellent
Notched R	+	−	−	−	−	−	Good	Excellent
R	+	−	+	−	+	−	Partial	Good
Notched R	+	+	+	−	+	?	Excellent	Partial
rS → Notched R	− → +	+ → −	−	+	−	+	Good	Partial

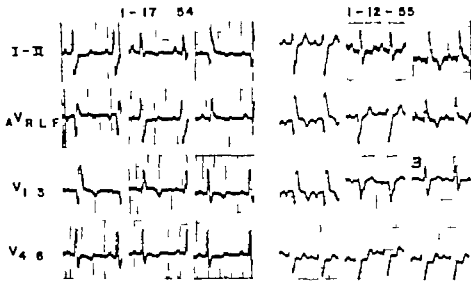


Fig 1 Electrocardiograms (Case 1 See text

leads revealed a large R wave and or a typical strain pattern of ST T or a marked left axis deviation (to more than −30 degrees) was present in the frontal plane The diagnoses of recent and old myocardial infarction were based on conventional criteria

Each heart was examined in a manner previously described In this method a semiquantitative histopathological study of the entire heart is made including the sinoatrial node the approaches to the sinoatrial node the atria the approaches to the atrioventricular node the atrioventricular node the atrioventricular bundle the bundle branches the peripheral Purkinje network and the entire ventricular myocardium The number of sections studied in each case is given in Table I The anatomic findings are presented in Table II Anatomic findings referable to hypertrophy recent or old bundle branch lesion and recent or old myocardial infarction in the right and left ventricles are correlated with the electrocardiographic interpretation in Table III

Report of cases

Case 1 (A 7 55) R G

CLINICAL DATA This 6? year-old white woman with history of diabetes mellitus for 10 years had several admissions to the Mount Sinai Hospital of Greater Miami in 1949 for control of the diabetes in 1953 for a kidney infection in March 1953 for myocardial infarction and in January 1953 and 1954 for episodes of acute pulmonary edema The last admission was January 1955 for acute left hemiplegia and pulmonary edema The blood pressure at that time was 210/110 mm Hg and the pulse rate was 120 per minute The patient died 9 hours after admission

ELECTROCARDIOGRAPHIC FINDINGS An electrocardiogram on J 7 1954 (Fig 1) revealed a rhythm at a rate of 8(I R of 0 16 second and QRS of 0 12 second QR complexes in the right precordial lead indicated the presence of right bundle branch block association with probable



Fig 2 Case 1 Section through second portion of right bundle branch showing fibrosis of about one third of its substance Weigert–van Gieson stain X150

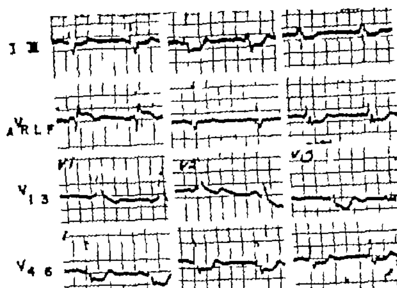


Fig 3 Electrocardiogram of Case See text

old antero-eptal infarction Small Q wa es in Lead II and prominent ones in Leads III and Vr sug gested the possibility of an old po terior wall infarct. The abnormal ST T contour was ttributable in part to digitalis In a record a year later (Jan 12 1948) (Fig 1) t the time of the last admi ion no substantial changes were noted except for a faster rate and less prominence of the alteratic attributed previously to involvement of the posterior wall by the infarction

POSTMORTEM EXAMINATION Aside from the find ings in the heart the pathologic diagnoses were (1) generalized arteriosclerosis and arteriolosclero- (2) intracerebral h morrhage severe (3) broncho- pneumonia severe and (4) pulmonary emphysema

Heart gross examination The heart eighed 475 grams Both entricles were hypertrophied the left more than the right There as marked sclerosis of the oronary arteries with arrowing in both the right circumflex and the anterior descend ing arteries The posterior wall of the left entricle was somewhat thinned and presented areas of scarification

Heart micro-copic examination *General path logic logy* There as generalized arteriolo-clerosis with acute and chronic organizing arteriolonecrosis th accompanying inflammatory changes in the atria and entricles and acute epicarditis *Left ventricle* There was an old infarct involving the inner part of the anterior and posterior walls and extending into the papillary muscles This was more marked in the apical half than in the basal half of the anterior all and in the posterior wall *Right ventricle* There as slight fatty infiltration in the anterior all with slight fibrosis ith a small scar in the po terior all *Ventricular septum* A subendocardial scar in olved most of the posterior septum and the apical half of the anterior septum I some area this pproached the right entricular endocardium There ere also some small organizing i ts at the base of the posterior septum *At se* septum The findings were tho-e of the

arteriolar necrosis and associated changes described pre ious ly

Conduction stem *S A* ode There was fibrosis and slight scar formation surrounding the artery of the node I addition there was a scattering of mononuclear cells within the node *Approaches to the S A node* There were small scars in the trial appendage adjacent to the all in addit to the vcular necro *Approa hes t the A V node* There was light infiltration of mononuclear cell which as part of the a culitis *A V node* There was light fibrosis and elasto *A V bu Dr pene trati g* There were no hanges *A V bundle branch*



Fig 4 Case Section through second portion of right bundle branch showing complete fibrosis and elastosis Weigert-van Gieson stain X80



Fig 3 Case 2 Section through the beginning of the third portion of right bundle branch bowing acute necro is of Purkinje fiber Hematoxylin eosin stain X60

g There w sl ght fibro of the right side of the branching bundle with mild acut degenerative changes Scattered mononuclear cell ere present t the bifurcation

Right bundle branch The fir t portion of the right bundle branch showed moderat fibrosis about one fifth to one third of ts sub tance being replaced by car ti ue The second portion w milarly scarified about one third to one half being replaced (Fig 2) The third portion showed marked fibros w th about three fourths replacement. The moderator band was not present for analysis I addition there were foci of irregular taining of the right bundle branch throughout its course with oc ca ional infiltration of neutrophils and mononuclear cells

Left bundle branch The left bundle branch howed minimal focal fibro is and occa ional acute degenerative changes w th an infiltration of mononuclear cell t parts of the termination of the left bundle branch

Blood pply to the conduction sy tem The ramus ostii cavae superioris showed no chan e The ramus septi fibrosi showed moderate narrowin There was moderate arteriolosclerosis and necrosis of the rteries nd arteri les of the septum

CARDIAC PATHOLOGIC DIAGNOSIS (1) Hyperten si e art rio-clerotic and arteriolosclerotic heart disease with severe narrowing of the anterior descending and right circumflex coronary arteries ( ) Old nfarct of the septum and ant rior and post rior w lls of the left ventricle w th small microscopic zones of orga izing infarcts n the posterior ptum t the base (3) Hypertrophy of the heart (left ventricle moderate right ventricle slight) (4) Marked fibros of the right bundle branch (5) Slight fibrosis of the inoatrial and atrioventricular nodes and the branching portion of the bundle (6) Acute generalized arteriol tis with nvolvement of the myocardium endocardium epicardium and the conduction syst m

Case 2 (1-87 56) S S

CLINICAL DATA This 68-year-old wh t man w th history f myocardial nfarction 12 years prior t dmi ion and an uneventful course following th was admitted t Mount Sinai Hospital on April 9 1956 He complained of udden onset of severe retrosternal pain which radiated to the left arm and was associated w th profuse d aphore is On adm sion he howed clinical evid nce of shock w th a blood pressure of 90/60 mm Hg and a pul e rat of 58 per minute A few r&l were noted at the lung base the heart sounds were d tant and no murmurs or rubs were detected Subsequently the blood pressure rose somewhat but the patient experienced recurrent chest pain lapsed t tractable hock and expired 1 hour after admis on

ELECTROCARDIOGRAPHIC FINDINGS The electrocardiogram (Fig 3) showed inus bradycardia of 58 w th a P R interval of 0 18 second and QRS of 0 1 second The contour of the P wa e uggested trial predominantly left sided pathology nd that of the ventricular complexe right bundle branch block probably in ociation with right entricular hypertrophy There were no characteristic alterations ttributable to previous infarct but there were features of acute coronary insufficiency with fresh subendocardial injury

POSTMORTEM EXAMINATION Aside from the find ings in the heart the pathologic diagno es were (1) generalized arteriosclero is (a) aorta (b) renal arteries ( ) pulmonary emphysema and fibrosis w th chronic passive hyperemia (3) fatty metamorphosis w th peripheral fibro of the liver (4) chronic splenic hyperplasia w th fibro is (5) arteriolosclerosis of the kidney and (6) hypertrophy of the prostate light

Heart gro examination The heart weighed 320 grams There was moderate hypertrophy of the right entricle w th slight hypertrophy of the left The coronary arteries howed severe sclero with narrowing especially of the right main coronary artery There was brown h red mushy thrombus 2 cm from the mouth of the left coronary artery There was white car measuring 3 by 2 by 3 cm involving the lateral portion of the po terior wall and the lateral wall of the left ventricle in ts basal two thirds



Fig 6 Case 2 Section through upper part of left bundle branch showing early necrotic changes Hematoxylin-eosin stain X150

Heart microscopic examination *General path ologic change* There was generalized arteriolo-sclerosis and arteriolonecrosis *Left ventricle* There as ery recent infarct th zones of organization involving all walls and the papillary muscles In addition there as an old scar in the lateral wall extending into the lateral parts of the anterior and posterior walls *Right ventricle* The abov mentioned recent infarct extended into the anterior and poste rior alls more into the latter *Ventricular septum* The abov mentioned recent infarct involved both the anterior and posterior parts of the septum ith occasional small scar formation on the left side *It an al atrial septum* These were involved in the recent infarct The right atrium in addition showed occasional small zones of organization and some fibrosis

Conduction system *S A node* There was some irregularity in staining and considerable arteriolo-sclerosis *Approaches to the S A node* There was ery recent infarct with small zones of organization of the atrial appendage with small organizing mural thrombus I addition sl ght fibrosis of the atrial appendage and the posterior crest was present. Fibrosis in the superior approaches to the S-A node was evident *Approaches to the A V node* There was slight fibrosis ith ery recent infarct. *A V node* Arteriolosclerosis of the node was apparent with unusual degenerative changes *A V bundle penetrat ng* There was slight fibrosis in the distal portion. *A V bundle b anching* Slight fibrosis was present in the beginning Small zones

degeneration and early necrosis ere present hich increased somewhat at the bifurcation

Right bundle branch Severe degenerati changes ere present in the first portion with light fibrosis In the second portion th fibrosis increased so that it replaced one third of the structure and the branch became completely necrotic. The fibrosis then in creased to about one half and thereafter there as almost complete fibrosis and elastosis of the right bundle branch (Fig 4) w th necrotic changes in the remainder Fatty infiltration ppeared with an infiltration of lymphoid cells The fibrosis then diminished but the necrosis appeared to be com plet as the right bundle branch lay in the region of the earl infarct of the septum I the third portion the necrosis as marked (Fig 5) and the fibrosis involved bout one half of the bundle accompanied by elastosis and fatty infiltration

Left bundle branch There was slight fibrosis of the beginning of the left bundle branch In addition many fibers showed degenerative changes and early necrosis (Fig 6) More apically there was marked fatty infiltration (Fig 7) There were areas in which onl a few Purkinje cells were seen in the midst of the fatty infiltration Still more distally the de-generative and early necrotic changes in the fibers of the left bundle branch increased

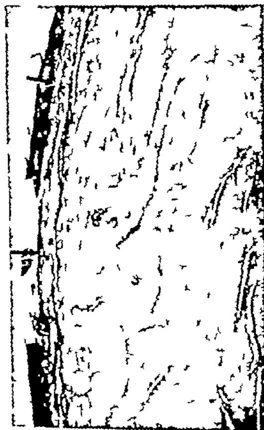


Fig 7 Case 2 Section through lower part of left bundle branch showing fibrosis and marked fatty infiltration Weigert-van Gieson stain X24

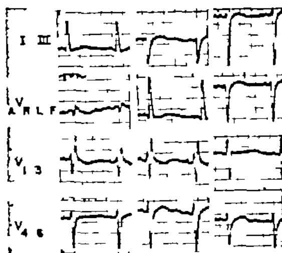


Fig. 8. Electrocardiogram of Case 3. See text.

Blood supply to the conduction system. The ramus ostii cavae superioris showed no change and the ramus septi fibrosi showed slight narrowing. There was marked narrowing of the arterioles of the septum but no change in the arteries.

CARDIAC PATHOLOGIC DIAGNOSES. (1) Arteriosclerotic heart disease with cor pulmonale with narrowing of the right main coronary artery and recent thrombus in the anterior descending coronary artery. (2) Old lateral wall infarct with extension to the anterior and posterior walls and small scars in the septum. (3) Very recent acute infarct involving the entire left ventricle, septum, and part of the right ventricle and parts of both atria. (4) Hypertrophy of the heart (right ventricle moderate, left ventricle slight). (5) Marked fibrosis of the right bundle branch with slight fibrosis of the left bundle branch. (6) Very early recent infarction of both bundle branches.

Case 3 (A 5 56) R. G.

CLINICAL DATA. This 56-year-old white woman was admitted to Mount Sinai Hospital on Feb. 3, 1956, because of intermittent epigastric pain which had been present for 3 weeks and which had become severe on the night prior to admission. There was a 10-year history of severe rheumatoid arthritis which had been treated with steroids for 4 years. Five years prior to admission she underwent a cholecystectomy for cholelithiasis. There was also a history of anemia requiring several blood transfusions about 9 months before admission.

On admission the patient was acutely ill with pallor and grunting respiration. The temperature was 98.6 F. but rose rapidly to 103 F. in 4 hours. The blood pressure was 112/82 mm. Hg, pulse 74 per minute, and respiratory rate 20 per minute. There was rigidity in the epigastrium with epigastric tenderness.

Within 24 hours after admission, edema and induration of the area under the cholecystectomy scar were noted. Incision and drainage of a large abscess in the right upper quadrant was performed on the second hospital day. After this procedure the temperature declined to a low-grade febrile level. Because of the clinical impression of adrenal exhaustion the patient was given daily intramuscular injections of 40 units of ACTH gel.

Nine days after admission the patient had a brisk hematemesis and lapsed into shock. Blood transfusions and levarterenol were given. The bleeding subsided over a 48-hour period but on the eleventh hospital day the patient had emesis of bright red blood and passed a copious tarry stool. Emergency laparotomy was performed and a large posterior duodenal ulcer was exposed. A limited gastric resection was accomplished. After surgery the patient developed right saphenous thrombophlebitis and had a septic temperature. She expired on Feb. 23, 1956, on the twentieth hospital day.

On admission the hemoglobin was 6.6 Gm. per cent, red blood count 2,900,000, white blood count 10,900 with 83 per cent neutrophils, 9 per cent band, 3 per cent lymphocytes, 3 per cent meta-



Fig. 9. Case 3. Section through second portion of right bundle branch showing fibrosis and fatty infiltration. Weigert-van Gieson stain, ×150.

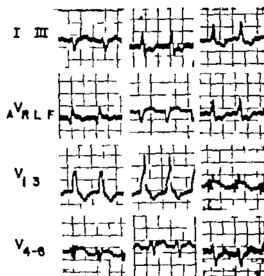


Fig 10 Electrocardiogram of Case 4 See text

myelocytes and 2 per cent myelocytes Urinalysis showed a trace of albumin numerous wh te blood cells and 2-4 red blood cell per high power field On February 8 the serum sodium was 147 5 mEq per liter potassium 3 28 mEq per liter nonprotein nitrogen 37 mg per cent total prote 5 6 Gm per cent albumin 3 5 Gm per cent and globulin 2 1 Gm per cent

ELECTROCARDIOGRAPHIC FINDINGS The electrocardiogram obtained on the fourth hospital day (Fig 8) 2 weeks before death showed sinus rhythm with a rate of 68 and P R of 0 12 second There as a marked left axis deviation in the frontal plane and shift of the precordial transition zone to the left suggesting left entricular hypertrophy On the other hand the contour of the right sided precordial lead in association th slurring and prolongation of QRS (to 0 12 second) suggested the presence of right sided intraventricular possibly bundle branch block The ST T configuration in limb nd precordial leads was abnormal and although not characteristic was considered con s tent ith left entricular strain

POSTMORTEM EXAMINATION Aside from the findings in the heart the pathologic diagnoses were (1) bleeding gastric ulcer with operativ procedures (2) dehiscence of gastrojejunostomy and duodenal stump (3) acute hepatitis and splenitis (4) acute adrenalitis (5) acute and chronic pyelonephritis (6) nephrosis (7) pulmonary emphysema and fibrosis (8) calculus in common bile duct t ampulla of V ter with marked dilatation of the common and hepatic bile ducts

Heart gross examination The heart weighed 380 grams The epicardium was grayish red dull and granular The endocardium of the right atrium was yellow The mitral and tricuspid alves showed mall gra erucous projections on the atrial aspect near the free margin There as slight left and right entricular hypertrophy The myocardium of the right trium showed an extensive zone of extending from the entrance of the inferior cava to the entrance of the superior vena cava and invol ng part of the sinoatrial nodal region There was practically no athero-sclerosis or narrowing of the large coronary arteries

Heart microscopic examination *General pathologic lesions* There was acute and subacute endocarditis of the mitral al e with associated myocarditis with abscesses and small infarcts and small organizing thrombi in the mall arteries This invol ed the anterior nd posterior wall of the left and right ventricles the entricular septum the left atrium and t lesser extent the trial septum *Right atr m* There was recent and organizing infarct of the right atrial ppendage with organizing f t necrosis and an organizing thrombus in one of the trial arterial branches and ssociated organizing pericarditis

Conduction system *S A node* The S-A node was nfiltrated by lymphoid cell *Approaches to the S A node* There was complete recent infarct nvolving all pproaches to the S-A node w th the exception of the superior pproaches *Approaches to the A V node* A recent infarct was present in the inferior approaches to the node *A V node* There were occasional macrophages in the node *A V bundle penetrati g* Th as the seat of mild and acute degenerative changes *A V bundle branching* This presented mild acute degenerative changes Occasional mononuclear cell surrounded the bundle There was moderate fibrosis of the right ide of the bifurcation

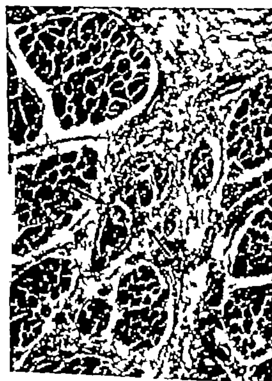


Fig 11 Case 4 Section through second portion of right bundle branch showing marked fibrosis and lesions Weigert-van Gieson stain ×150

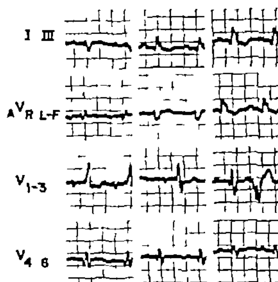


Fig 1 Electrocardiogram of Case 5 See text

Right bundle branch I the first portion there was moderate fibrosis about one fifth of the structure being replaced This was accompanied by focal acute degenerative changes and scattering of mononuclear and lymphoid cells I the second portion there was progressive increase in the acute degeneration and early necrosis as it proceeded distally The amount of fibrosis increased to about one-fourth replacement of the structure (Fig 9) then decreased more distally I the mid t of the second portion considerable fatty infiltration appeared (Fig 9) The right bundle branch became divided into several parts lying in fatty tissue with marked increase in acute degenerative change I the third portion the right bundle branch showed marked fatty infiltration and a light infiltration of lymphoid cell

Left bundle branch The beginning of the left bundle branch showed considerable acute degeneration and early necrotic change more intense than in the beginning of the right bundle branch with light infiltration of mononuclear cell This became more intense distally with considerable focal necrosis and fatty infiltration

Blood supply to the conduction system The ramus ostii cavae superioris and the ramus septi fibrosi showed no change The arteries and arterioles of the septum showed acute vascular degeneration

CARDIAC PATHOLOGIC DIAGNOSES (1) Acute and subacute endocarditis of the mitral valve with associated myocarditis with abscesses and small infarcts (2) Organizing thrombus in a right atrial artery with organizing infarct of the right atrium (3) Acute vascular degeneration (4) Acute fibrinous pericarditis (5) Fibrosis of the right bundle branch moderate (6) Acute degenerative and early necrotic changes of both bundle branches moderate (7) Acute and organizing infarction of the approaches to the sinoatrial and atrioventricular nodes

Case 4 (1 125 5?) H R.

CLINICAL DATA This 65 year-old white man with long-standing history of angina pectoris and atrial fibrillation was admitted to the Mount Sinai Hospital on June 24 1955 with severe pain and numbness of the left leg of 8 hours duration There was no history of previous claudication On admission the patient was acutely ill with cyanosis and profuse diaphoresis The apical rate was 140 and the respirations were 50 per minute The heart was not enlarged An abdominal aortic pulse was palpated faintly but all pulses distal to this area were absent There was a bluish discoloration and mottling of both lower extremities extending to the lower abdominal wall on the right Despite vasopressor amines and intravenous dextran the patient expired in shock 1½ hours after admission

On admission the hemoglobin was 13.73 Gm per cent the red blood count was 4.45 million and the white blood count was 5,600 with a normal differential

ELECTROCARDIOGRAPHIC FINDINGS The electrocardiogram (Fig 10) revealed rapid and regular ventricular action at a rate of 136 caused by an ectopic atrial tachycardia possibly atrial flutter with a 2:1 ventricular response There was a pattern of a right bundle branch block (QRS of 0.12 second) in association with right ventricular hypertrophy ST T deviations in the precordial leads suggested recent injury effects in the anteroseptal region but there was no evidence of myocardial necrosis due to confluent infarct

POSTMORTEM EXAMINATION Aside from the findings in the heart the pathologic diagnoses were (1) chronic passive hyperemia fibrosis and edema of the lungs (2) bilateral hydrothorax (3) chronic passive hyperemia and peripheral fibrosis of the liver (4) severe atherosclerosis of the aorta and



Fig 13 Case 5 Section through distal part of second portion of right bundle branch showing almost complete replacement by fibrous and elastic tissue Weigert–van Gieson stain X80

iliac arteries (5) recent and organizing thrombi of the abdominal aorta and iliac arteries (6) subacute splenitis

Heart gross examination The heart weighed 500 grams The left ventricle was markedly hypertrophied and the right was moderately hypertrophied There was severe atherosclerosis with almost complete occlusion of the left circumflex and anterior descending coronary arteries and marked narrowing of the ostium of the right coronary artery In addition the left anterior descending coronary artery presented a recent thrombus 3 to 4 cm from its ostium which completely occluded the lumen An infarct of uncertain age was noted in the posterior septum and in the subendocardial portion of the anterior and posterior walls petering out toward the lateral wall.

Heart microscopic examination *General pathologic changes* There was generalized arteriosclerosis and necrosis *Left ventricle* There was an old subendocardial infarct with foci of organizing infarct spread throughout both the anterior and posterior wall with a superimposed very early recent subendocardial infarct *Right ventricle* There was an old and organizing infarct involving the anterior and posterior walls more marked in the posterior than in the anterior walls and less marked than in the left ventricle. *Ventricular septum* There was an old and organizing mostly subendocardial infarct on the left ventricular side which extended through the wall in some areas in both the anterior and the posterior parts In addition there was a very recent infarct more severe in the posterior than in the anterior septum *Right atrium* There were old and organizing zones of infarction *Left atrium* There was an old subendocardial infarct with foci of acute degeneration *Atrial septum* Fibrosis with focal fat necrosis was present

Conduction system *S A node* There were no changes *Approaches to the S A node* There was marked fibrosis with small scars involving the superior and medial connections and to a lesser extent the inferior connections There was organizing fat necrosis around the S-A node. *Approaches to the A V node* There were no changes *A V node* There were scattered mononuclear cells at the beginning of the node At the end there was minimal fibrosis *A V bundle penetrating* There was fibrosis at the distal portion with some irregularity in staining of the fibers with mononuclear cells on the periphery *A V bundle branching* There was considerable fibrosis in the bundle with foci of early necrosis and frank necrosis at spots of junction of the fasciculi of the left bundle branch

Right bundle branch The beginnings of the first portion presented increased elastosis followed by small areas of fibrosis In this region there were acute degenerative changes but no frank necrosis In the second portion the fibrosis and elastosis increased markedly (Fig 11) with reduction of 50 per cent of its parenchyma this became less more distally In the third portion severe acute degenerative changes but no necrosis persisted to the end

Left bundle branch There were acute degenerative changes and early necrosis of many fasciculi at the junction with the bundle throughout the entire posterior radiation Degenerative and/or necrotic changes in the Purkinje fiber were present throughout the bundle branch including the periphery

CARDIAC PATHOLOGIC DIAGNOSES (1) Arteriosclerotic and arteriolosclerotic heart disease with marked narrowing of the left circumflex and anterior descending coronary arteries and narrowing of the ostium of the right coronary artery (2) Recent thrombus in the anterior descending coronary artery (3) Old subendocardial infarct of the septal anterior and posterior wall of the left ventricle and extension into the anterior and posterior walls of the right ventricle (4) Focal organizing infarct of these walls (5) Very recent subendocardial infarct of the anterior septal and posterior wall of the left ventricle (6) Marked hypertrophy of the left ventricle and moderate hypertrophy of the right (7) Moderate fibrosis of the atrioventricular bundle (8) Moderate fibrosis and elastosis of the right bundle branch with moderate acute degenerative changes (9) Marked acute degeneration and early necrosis (focal) of the left bundle branch

Case 5 (A 409 55) M A

CLINICAL DATA This 6 year-old white man was admitted to Mount Sinai Hospital on May 3 1955 in congestive failure He had had pneumonia 6 weeks previously for which he had been admitted to another hospital After his discharge he had noted progressive swelling of the legs and swelling of the abdomen with moderate shortness of breath

On examination the blood pressure was 108/60 mm Hg and the pulse was 88 and regular The heart was enlarged to the left with bilateral rales and pleural effusion There was massive ascites and marked edema of the lower extremities The patient showed some improvement on digitalis and diuretics but suddenly and unexpectedly died in shock on June 9 195 The nonprotein nitrogen on admission was 60 and the urinalysis showed 1 plus albumin

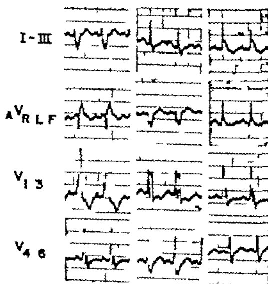


Fig 14 Electrocardiogram of Case 6 See text

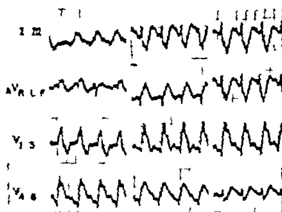


Fig. 16. Electrocardiogram of Case 7. See text.

Heart, gross examination. The heart weighed 440 grams. There were moderate hypertrophy and dilatation of the right atrium and ventricle and slight hypertrophy of the left atrium and ventricle. The right coronary artery 3 cm from its origin was completely occluded by atheromatous plaques and what appeared to be a recent thrombus. The left coronary artery showed atherosclerosis but no narrowing. There was a yellowish mottling of the endocardial surface of the left side of the septum and anterior and posterior walls of the left ventricle.

Heart, microscopic examination. *General pathologic change:* There was generalized acute vascular degeneration. The point of obstruction in the right coronary artery showed a recent and organizing thrombus. *Left ventricle:* There was minimal fibrosis of the anterior wall and slight fibrosis of the posterior wall. *Ventricular septum:* There was slight fibrosis with small scars in the anterior and posterior septa. *Right ventricle:* There was moderate fibrosis with small scars in the anterior and posterior walls. *Atria and atrial septum:* There was slight fibrosis and elastosis of the right atrium and septum and slight fibrosis of the left atrium.

Conduction system. *S-A node:* There was no change. *Approaches to the S-A node:* Slight fibrosis was noted. There was a small scar directly adjacent to the S-A node. *Approaches to the A-V node:* There was slight fibrosis in the upper and lower approaches. There was an occasional focus of macrophages immediately adjacent to the node. *A-V node:* There was minimal fibrosis. *A-V bundle, penetrating:* There was minimal fibrosis. *A-V bundle, branching:* There was a slight infiltration of macrophages.

Right bundle branch. The beginning of the right bundle branch showed an infiltration of macrophages. In the second portion the structure first showed slight fibrosis (Fig. 15A) and then rapidly it became completely fibrotic (Fig. 15B). The completely fibrotic lesion measured only 0.2 mm. After this lesion the right bundle branch became normal again. More peripherally in the second portion there were occasional macrophages around the structure with fatty infiltration. In the third portion slight acute degenerative changes appeared with an infiltration of lymphoid cells and mononuclear cells.

Left bundle branch. There was a focal infiltration of macrophages. More peripherally there was considerably fatty infiltration.

Blood supply to the conduction system. The ramus ostii cavae superioris, the ramus septi fibrosi, and the arteries and arterioles of the septum showed no narrowing.

CARDIAC PATHOLOGIC DIAGNOSES. (1) Arteriosclerotic heart disease with recent and organizing thrombus with obstruction of the right main coronary artery. (2) Moderate fibrosis of the septum and anterior and posterior walls of the right ventricle and slight fibrosis of the anterior and posterior walls of the left ventricle. (3) Acute vascular degeneration. (4) Hypertrophy of the heart (right ventricle moderate, left ventricle minimal). (5) Slight fibrosis of the approaches to the sinoatrial node and minimal fibrosis of the atrioventricular node and bundle. (6) Marked fibrosis of the right bundle branch. (7) Slight acute degenerative changes of both bundle branches. (8) Fatty infiltration of both bundle branches.

Case 7 (A 175-55) S.I.

CLINICAL DATA. This 62-year-old white woman was admitted to Mount Sinai Hospital on Oct. 2, 1955, with a history of retrosternal pressure associated with diaphoresis of 3 days' duration increasing in severity on the day of admission.

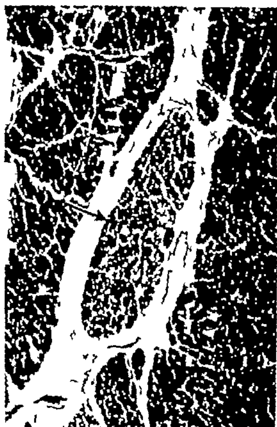


Fig. 17. Case 7. Section through the right bundle branch showing early necrosis surrounded by recent infarct of the myocardium. Hematoxylin-eosin stain. X93.

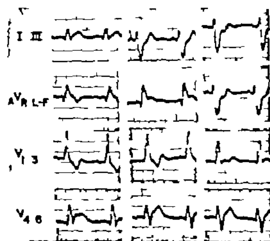


Fig. 18 Electrocardiogram of Case 8. See text.

Past history revealed no indication of heart disease. A carcinoma had been detected on radical mastectomy 2½ years previously and the patient was receiving testosterone for bony metastases to the pelvis. On admission she was in shock, cyanotic, had coarse rales in both lung fields and the neck veins were distended. She expired 1½ hours after admission.

ELECTROCARDIOGRAPHIC FINDINGS. The electrocardiogram (Fig. 18) showed sinus tachycardia (rate of 136 and P-R of 0.18 second) with premature ectopic beats probably of ventricular origin frequently occurring in pairs. The ventricular complexes had bizarre appearance with characteristic features of both right bundle branch block (QRS of 0.14 second) and recent anterior and lateral wall infarction. The predominance of R waves in the right precordial lead was ascribed to right ventricular hypertrophy.

POSTMORTEM EXAMINATION. Aside from the findings in the heart, the pathologic diagnoses were (1) radical mastectomy for carcinoma of the breast, (2) metastasis to the third lumbar vertebra, (3) hirsutism, (4) pulmonary fibrosis and arteriolosclerosis and ( ) adenoma of the thyroid.

Heart gross examination. The heart weighed 290 grams. There was questionable hypertrophy of both ventricles. There was marked thickening and narrowing of the beginning of the anterior descending artery. At one point a red thrombus completed the occlusion. The other arteries showed no narrowing. The myocardium of the left ventricle in the most superior portion of the anterior wall presented a distinct area of softening and there were slight hemorrhagically discolored zones in the anterior wall adjacent to the septum.

Heart microscopic examination. *General pathologic change.* There was generalized acute arteriolitis and periarteriolitis. Focal small zones of metastases with organizing myocarditis involving the left ventricle anteriorly and posteriorly and the septum were noted. *Left ventricle.* In addition to the abovementioned features there was irregularity in staining of fibers in the anterior wall less in the posterior wall. *Right ventricle.* There was some irregularity in staining in the anterior wall at the base and in the inferior wall. *Ventricular septum.* In addition to the general changes described above there was fibrosis of the right side of the septum at the base posteriorly and generalized fibrosis anteriorly. There was also irregularity in staining of the fibers more marked anteriorly. *Atria and atrial septum.* There were no remarkable changes.

Conduction system. *S-A node.* There were no changes. *Approaches to the S-A node.* There was an occasional small zone of organizing infarction. *Approaches to the A-V node.* There was no appreciable change. *A-V node.* There was some lymphoid cell infiltration with slight fibroblastic proliferation. *A-V bundle penetrating.* There was no appreciable change. *A-V bundle branching.* In the beginning there was slight fibrosis of the right side of the bundle which became moderate at the bifurcation.

Right bundle branch. The first portion showed light fibrosis. The second portion lay in an area of acute degenerative changes of the myocardium and the right bundle branch itself showed severe acute degenerative changes (Fig. 19). This persisted to the moderator band.

Left bundle branch. In the beginning there was light fibrosis. Throughout its course it showed light acute degenerative changes.

Blood supply to the conduction system. In the ramus ostii cavae superioris there was no narrowing; in the ramus septi fibrosi there was moderate narrowing. In the arteries and arterioles of septum there was marked arteriolosclerosis with narrowing.

CARDIAC PATHOLOGIC DIAGNOSES. (1) Arteriosclerotic heart disease with recent thrombus in the anterior descending coronary artery. (2) Very recent anteroseptal ischemic changes. (3) Focal small metastases of carcinoma of the breast to the myocardium with focal organizing myocarditis. (4)

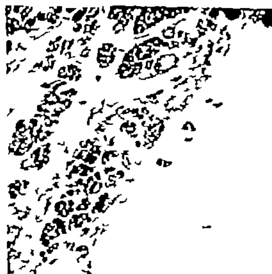


Fig. 19 Case 8. Section through second portion of right bundle branch showing fibrous necrosis and infiltration of neutrophils. Hematoxylin-eosin stain. ×115.



Fig 20 Case 8 Section through Purkinje fibers of left bundle branch showing necrosis Hematoxylin-eosin stain ×340

Acute arteriolitis and periarteriolitis. (5) Slight fibrosis of the right side of the atrioventricular bundle branching (6) Severe acute degenerative changes of the right bundle branch and slight acute degenerative changes of the left bundle branch

Case 8 (A 9 55) M O

CLINICAL DATA. This 67 year-old white man was admitted to Mount Sinai Hospital on May 14 1955 with history of gradually increasing pain in both elbows of 3 days duration followed by *sudden onset of severe prostrating substernal distress* associated with diaphoresis and dyspnea There was no previous history of precordial distress He was critically ill on admission and in peripheral vascular collapse. Despite the use of lanatoside C and levarterenol to combat shock and failure the patient failed to respond expiring 8 hours after admission The white blood count was 20 5 0 with 78 per cent neutrophils 6 per cent band 13 per cent lymphocytes 2 per cent monocytes and 1 per cent myelocytes. The red blood count was 6 350 000 with a hemoglobin of 17 6 Gm per cent.

ELECTROCARDIOGRAPHIC FINDINGS The electrocardiogram (Fig 18) showed a sinus rhythm at a rate of 73 with a P R of 0 14 second The QRS was prolonged to 0 16 second with features of right bundle branch block and right ventricular hypertrophy in the precordial lead However marked left axis deviation with small QRS complexes in Leads I and aV$_L$ also suggested left ventricular hypertrophy with anterolateral wall infarction S-T deviations in precordial lead indicated that the infarct at least in its lateral part was of recent date

POSTMORTEM EXAMINATION Aside from the findings in the heart the pathologic diagnoses were (1) pulmonary edema bilateral with early bronchopneumonia and (2) fatty metamorphosis of the liver

Heart gross examination The heart weighed 540 grams Both the left and right ventricles were markedly hypertrophied The subendocardial half of the entire anterior wall of the left ventricle the left aspect of the entire ventricular septum and the adjacent portion of the posterior wall were *diffusely hemorrhagically discolored* A small area of hemorrhage measuring 1 0 cm in greatest dimension was noted in the myocardium of the anterior wall of the right ventricle The right coronary artery was the dominant artery and presented moderate sclerotic changes but no narrowing The left anterior descending artery showed severe sclerotic changes and was occluded by a fresh thrombus 2 0 cm from the ostium The left circumflex artery was likewise occluded by an organizing thrombus near its ostium

Heart microscopic examination *General pathologic changes* There was diffuse acute arteriolar degeneration and acute pericarditis The acute infarct present in the various walls was typified by marked hemorrhage and an infiltration of neutrophils *Left ventricle* Most of the anterior wall and parts of the posterior wall were involved in the acute infarct. *Right ventricle* The anterior wall showed foci of acute infarct. In addition there was an occasional scar and zone of fibrosis. The posterior wall showed only a small zone of recent infarct There were occasional zones of fibrosis with small

scars Both walls showed marked fatty infiltration *Ventricular sept m* The entire septum was involved in the acute infarct I addition mall zones of organizing infarct ere noted subendocardiall m the posterior portion There were also small scars on the right side of the septum proximally and throughout the septum distally w th considerable fibrosis

Conduction system *S-A node* There was no change *Approaches to the S A node* The posterior crest showed slight fibrosis *A V node nd its pproaches* There were no changes *A V bundle penet ating and branching* There were no changes

Right bundle branch The first portion showed little change The second portion showed con ider able fibrosis with necrosis and an infiltration of neutrophils (Fig 19) The recent infarct permeated in the third portion

Left bundle branch As the left bundle branch proceeded di tally there was increasing acute degeneration going on to frank necrosis (Fig 20) with an infiltration of neutrophil

CARDIAC PATHOLOGIC DIAGNOSES (1) Coronary sclerosis th severe narrowing of the anterior descending artery ( ) Recent thrombus with oc clusion of the anterior descending artery and organ izing thrombus of the left circumflex artery (3) Focal fibrosis with small scars of the posterior septum and right ventricle (4) Massi recent hemorrhagic infarct involving the entire ventricular septum anterior wall and the apex maximally the posterior all moderately and the anterior and posterior walls of the right ventricle slightly (5) Recent infarction of both bundle branches (6) Moderate fibrosis of the right bundle branch (7) Marked hypertrophy of both ventricles

Case 9 (A 182 55) G S

CLINICAL DATA This 0-year-old white man known to ha been hypertensive for 20 years a admitted to the hosp tal on Jan 2 1955 because of protracted chest pain For 2 years prior to admi sion the patient had show signs and symptoms of congestive heart failure which was relieved by digitalization periodic mercurial diu retics and bed rest Angina which had existed for 1 year usually occurred after meals and was relieved by nitrogl cerin On the night of admission the patient wa wakened by protracted precordial distress and he entered the hospital in collapse On examination he complained of severe chest pain was in severe distress cold and clammy The blood pressure was 110/ 0 mm Hg the ventric ular rate as 140 and gros ly irregular The heart was enlarged to the left and a systolic murmur was heard t the apex maximally Bibasilar rales were present On the da of admission the patient lapsed into more severe shock requiring levarterenol for 2 days to maintain hi blood pres ure Progres iv improvement occurred and he was discharged on March 15 1955 pproximately 7 weeks after admission After di-charge he experienced angina on light emotional or physical provocation and suffered recurrent congestive failur Three day prior to his last admission his substernal pain increased in frequency and inten ity and was nrelieved by nitroglycerin At this time he was given Demerol oxygen and mercurial diuretics with some elief He was readmitted to the hospital on Oct 10 1955 th severe dyspnea and protracted chest pain On admission he was pulseless in prof und hock sem tuporou cyanotic w th Cheyne Stokes respirations He failed to espond to vasopr sor therapy and expired 5 hours after admission.

ELECTROCARDIOGRAPHIC FINDING The electro-cardiograms (Fig 21) during the patient first admis ion taken on Jan 22 19 5 showed at first atrial fibrillation with rapid entricular espon e (a eraging 130 per minute) and later on Feb 8 1955 sinus rhythm t ate of 80 th P R of 0 14 second Ther were signs f left entricular hyper trophy and of an incomplete left bundle branch

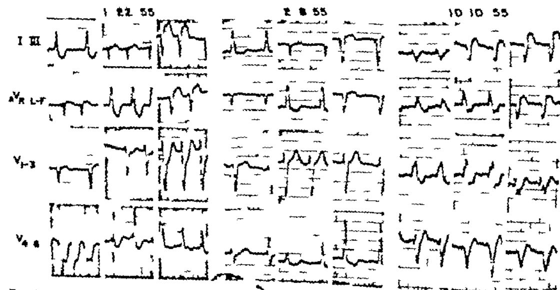


Fig 21 Electrocardiogram of Case 9



Fig. 22. Case 9. Section through bifurcation into right bundle branch and anterior radiation of left bundle branch showing old scar. Weigert-van Gieson stain. ×25.

block (QRS of 0.12 second). On January 22 these appeared to be modified by fresh injury of the posterior wall but changed later on February 8 to alterations consistent with posterior wall infarction.

In the last record taken on Oct. 10, 1955 during the final admission there was sinus tachycardia of 110 with slightly prolonged P-R interval (0.22 second). The contour of the ventricular beats had changed to that of right bundle branch block (QRS of 0.16 second) associated with right ventricular hypertrophy and appeared to be modified by digitalis and/or recent posterior wall injury. Left ventricular hypertrophy and the left-sided intraventricular block were no longer evident.

POSTMORTEM EXAMINATION. Aside from the findings in the heart, the pathologic diagnoses were: (1) arteriolar nephrosclerosis with acute vascular degeneration and early necrosis; (2) generalized arteriolar sclerosis and acute vascular degeneration and early necrosis; (3) marked pulmonary emphysema with fibrosis and pulmonary arteriolosclerosis; (4) chronic passive hyperemia of the liver with central necrosis and periportal fibrosis; (5) chronic passive hyperemia of the spleen with fibrosis; (6) bronchopneumonia; (7) chronic pancreatitis; and (8) chronic adrenalitis and periadrenalitis.

Heart gross examination. The heart weighed 500 grams. There was a diffuse fibrinous exudate over the heart. There was marked hypertrophy of both ventricles and relatively greater hypertrophy of the right ventricle. An old infarct with aneurysmal dilatation was noted in the basilar half of the posterior wall and the most basilar part of the posterior septum. In addition, a recent infarct was present involving the entire septum extending through to the right ventricle and extending over the apical third of the posterior septum and the apical two thirds of the anterior septum in which region it also involved the lateral wall. It also extended to the apical two fifths of the anterior and the inferior wall of the right ventricle. There was a small mural thrombus in the left ventricle. There was marked sclerosis of the coronary arteries with narrowing of the anterior descending and the right main artery with a recent thrombus at the beginning of the anterior descending branch.

Heart microscopic examination. *General pathologic changes.* There was marked arteriosclerosis and arteriolosclerosis of the coronary arteries. *Left ventricle.* There was an old infarct involving most of the subendocardial regions of the left ventricle. In some areas in the posterior wall this extended intramurally and occasionally subepicardially. In addition, there was a recent infarct in both the anterior and posterior wall. *Right ventricle.* The recent infarct extended into the anterior and posterior walls. In addition, there were foci of organizing and old infarction in the anterior and posterior wall. *Ventricular septum.* Most of the septum was involved in the recent infarct. In addition, the left ventricular subendocardial portion showed an old infarct. *Atria and atrial septum.* Many regions of the right atrium showed areas of recent and organizing infarcts, whereas the left atrium and septum showed recent infarct.

Conduction system. *S-A node.* There was acute degeneration and early necrosis. *Approaches to the S-A node.* The posterior crest showed many zones of recent organizing and old infarction. Likewise Wenckebach bundle and the myocardium at the inferior approaches to the node showed many areas of recent infarction. There were some acute degenerative changes of the myocardial fibers at the approaches to the A-V node but no frank infarction. *A-V node.* There were no changes. *A-V bundle penetrating.* There were no changes. *A-V bundle branching.* There were acute degenerative changes at its junction with the left bundle branch fascicuh. Also an organizing infarct involving part of the cross section of the bundle was present. In other spots there was fibrosis. A scar was noted at the left side of the bifurcation (Fig. 22) which, however, did not interrupt the bundle.

Right bundle branch. In the first portion there was moderate fibrosis with acute degeneration of its fibers. In the second portion there was early necrosis. In the third portion there again was early necrosis (Fig. 23) as it lay in a recent infarct.

Left bundle branch. The beginning of the left bundle branch showed acute degenerative changes. Slightly more distally it was the seat of early necrosis as it lay in the midst of an acute infarct. Throughout the remainder of its course there was focal fatty infiltration. Here and there Purkinje fibers showed necrosis and zones of fibrosis.

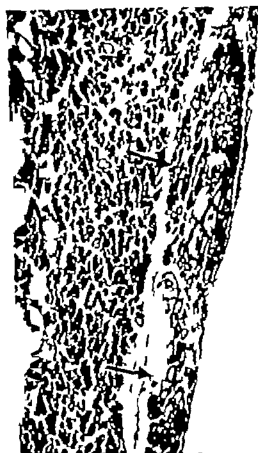


Fig 23 Case 9 Section through third portion of right bundle branch Hematoxylin-eosin stain ×68

Blood supply to the conduction system The ramus ostii cavae superioris showed no changes. The ramus septi fibrosi showed marked sclerosis with narrowing The arterioles of the septum showed narrowing

CARDIAC PATHOLOGIC DIAGNOSES (1) Marked coronary sclerosis with severe narrowing of the right coronary artery in the region of the ramus ostii cavae superioris left anterior descending artery and ramus septi fibrosi (2) Recent thrombus in the anterior descending artery (3) Massive old subendocardial infarct involving the posterior walls of both ventricles the left ventricular side of the septum with less involvement of both anterior wall (4) Massive recent infarct, involving both anterior wall most of the septum with less involvement of both posterior wall (5) Organizing and old scar of the branching portion of the bundle of His with acute degenerative changes (6) Focal necrosis of the sinoatrial node (7) Acute degeneration and early necrosis of both bundle branches

Discussion

In an attempt to correlate anatomic lesions of the bundle branches with bundle branch block patterns of the electrocardiogram it must be emphasized that the term complete bundle branch block used in routine electrocardiography does not of necessity imply a complete anatomic disruption of the continuity of one of the bundle branches Conceivably a unilateral delay of impulse conduction through a functionally altered portion of a bundle branch could produce in the electrocardiogram the pattern of a complete bundle branch block if this retardation exceeds the time necessary for spread of impulses from the contralateral ventricle through the ventricular septum The latter time has been estimated to be between 0 04 and 0 06 second[11, 12] Hence the term complete bundle branch block has to be understood in a functional rather than a strictly anatomic sense

With this reservation in mind we can divide for the purpose of correlation the 9 cases of our series into three groups (1) cases in which the electrocardiographic findings of complete right bundle branch block (RBBB) must be correlated with old lesions in the right bundle branch (Cases 1 3 5 6) (2) cases in which the correlation must be made with recent and old lesions (Cases 2 4 8 9) and (3) cases in which the correlation must be made with recent lesions (Case 7)

In Group 1 there is electrocardiographic evidence that complete RBBB was present 1 year (Case 1) 1 month (Case 5) and 2½ weeks (Case 3) before death *In all of these* old lesions in the right bundle branch were found In Case 6 the electrocardiogram showing complete RBBB was taken within 24 hours of death Since no recent lesion is present in the right bundle branch in this case the correlation is again made with the old lesion present Here then we have excellent correlation between the electrocardiographic complex and an old lesion in the right bundle branch In Group 2 the electrocardiogram showing complete RBBB was taken within 24 hours of death and the length of time the RBBB might have been present is unknown Hence all lesions present in the right bundle branch must be correlated with this complex In all 4 cases (Cases 2 4 8 9) significant lesions in the right bundle branch were found If the RBBB was of recent vintage then the correlation is excellent If it was long

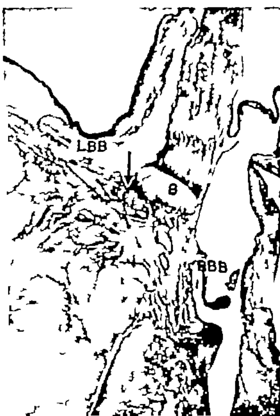


Fig 22 Case 9 Section through bifurcation into right bundle branch and anterior radiation of left bundle branch showing old scar Weigert–van Gieson stain ×25

block (QRS of 0 12 second) On January 22 there ppeared to be modified by fresh injury of the posterior w ll but changed later on February 8 to lterations consistent with posterior wall in farction

I the last record taken on Oct. 10 1955 during the final adm sion there was a sinus tachycardia of 110 with a slightly prolonged P R interval (0 22 second) The contour of the entricular beats had changed to that of a right bundle branch block (QRS of 0 16 second) associated w th right entricu lar hypertrophy and appeared to be modified by digitalis and/or ecent posterior wall njury Left entricular hypertrophy and the left sided intraven tricular block were no longer evident

POSTMORTEM EXAMINATION Aside from the find ings in the heart the pathologic diagnoses were (1) arteriolar nephrosclerosis with acute ascular degeneration and early necros (2) generalized arteriolar scleros and acute vascular degeneration and early necrosis (3) marked pulmonary emphy sema w th fibrosis and pulmonary arteriolosclerosis (4) chronic pas n hyperemia of the li er w th central necrosis and periportal fibrosis ( ) chronic pas n hyperemia of the pleen w th fibros (6) bronchopneumonia (7) chronic pancreatiti and (8) chronic adrenalitis and periadrenalitis

Heart gross examination The heart weighed 500 grams There was diffuse fibrinous exudate over the heart There was marked hypertrophy of both ventricles and a relatively greater hypertrophy of the right entricle An old infarct with aneurysmal dilatation was noted in the b ilar half of the poste rior wall and the most ba lar part of the posterior septum I addition a recent infarct was present n ol ing the entire septum extending through to the right entricle and extending over the apical third of the posterior septum and the apical t third of the anterior septum in which region it also involved the lateral wall It also extended to the apical t o fifths of the anterior and the inferior walls of the right ventricle There was a small mural thrombu in the left ventricle There was marked sclerosis of the coronary arteries with narrowing of the anterior descending and the right main artery with a recent thrombus at the begin ning of the terior descending branch

Heart microscopic examination *General path ologic cha ge* There was marked arteriosclerosis and arteriolosclerosis of the coronary arteries *Left ventricle* There was an old infarct invol ing most of the subendocardial region of the left entricle I some areas in the posterior wall this extended intramurally and occa ionall subepicardially I addition there was recent infarct in both the anterior and posterior walls *Right ventricle* The recent infarct extended into the anterior and poste rior wall I addition there were foci of organizing and old infarction in the anterior and posterior walls *Ventricular septum* Most of the septum wa involved in the recent infarct I addition the left ventricular subendocardial portion showed an old infarct *Atria nd atrial sept m* Many regions of the right trium showed areas of recent nd organiz ing infarcts whereas the left tri m and septum showed recent infarct

Conduction system *S A node* There was acut degeneration and early necrosis *Approaches to the S A node* The posterior crest howed many zones of recent organizing and old infarction Likewise Wenckebach bundle and the myocardium t the inferior approaches to the node showed many areas of recent infarction There were some acute de generati changes of the myocardial fibers t the approaches to the A V node but no frank infarction *A V node* There were no changes *A V bundle penetrating* There were no changes *A V bundle branching* There were acute degenerati changes at ts junction w th the left bundle branch fasciculi Also an organizing infarct involving part of the cros section of the bundle was present I other spots there was fibrosis A scar was noted t the left side of the bifurcation (Fig 22) which however did not interrupt the bundle

Right bundle branch In the first portion there was moderate fibrosis w th acut degeneration of its fibers I the second portion there was early necrosis I the third portion there again was early necrosis (Fig 23) as t lay in recent infarct

Left bundle branch The beginning of the left bundle branch showed acute degenerative changes Slightly more distally t was the seat of early necrosis as it lay in the mid t of an acute infarct Throughout the remainder of ts course there was focal fatty infiltration Here and there Purkinje fibers showed necrosis and zones of fibrosis

rates in general the monumental work of Lenègre.[1] There is a slight point of variance. In our series, as in the work of Mahaim[14] and Yater, both bundle branches were involved in complete right bundle branch block whenever correlation was made with recent lesions.

Electrocardiographically, the presence of a right bundle branch block was reflected in the right precordial leads in 6 cases by a more or less slurred R wave and in 3 by an rR' or qR complexes (Table II). This does not conform with the usual frequency of these patterns, the latter two being ordinarily the more common ones. Two anatomic features predominating in the material studied may be responsible for this, namely, recent and old extensive infarction of the left ventricle or right ventricular hypertrophy. The absence of myocardial infarction in Case 3, the only one with an rSR' pattern, could indeed suggest a dependence of the QRS configuration over the right precordium on the condition of the myocardium of the left ventricle. However, in Case 5, with another common pattern (rR'), massive left ventricular infarction was present. Kossmann and associates[17] have pointed out that it is virtually impossible to visualize a situation in which, in the presence of arteriosclerotic heart disease, so much destruction could occur that, from the standpoint of muscle mass alone, the right ventricle would predominate over the left. Therefore, it appears more likely that the presence to a varying degree of right ventricular hypertrophy in all of the cases was the factor which determined the QRS configuration of the right precordial leads in the material presented.

In contrast to the accuracy in the diagnosis of right ventricular hypertrophy, 5 cases with anatomically left ventricular hypertrophy could not be recognized as such electrocardiographically, and 1 case (Case 7) in which such a diagnosis was made showed only a slight degree at autopsy. Furthermore, in Case 9 an incomplete left bundle branch block associated with left ventricular hypertrophy (demonstrated at autopsy) completely disappeared after the development of a right-sided ventricular conduction defect. It would appear, therefore, that in arteriosclerotic heart disease the combination of a complete right bundle branch block with right ventricular hypertrophy can entirely obscure electrocardiographic manifestations of left ventricular hypertrophy, with or without an incomplete left bundle branch block.

Summary

1. The conduction system and the entire heart in 9 cases in which the electrocardiographic pattern was that of complete right bundle branch block were studied histopathologically. Eight of these cases were instances of coronary heart disease and one of myocarditis.

2. There was positive correlation between the electrocardiographic pattern of complete right bundle branch block and the presence of significant pathologic changes in the right bundle branch.

3. There was no correlation with any other pathologic finding in the heart.

4. Thus, the electrocardiographic pattern of complete right bundle branch block has an anatomic base in significant lesions in the right bundle branch in coronary heart disease. The anatomic base of this complex in congenital or other types of heart disease is not discussed in this work.

5. Right ventricular hypertrophy was correctly diagnosed electrocardiographically in the presence of complete right bundle branch block. In coronary heart disease the combination of complete right bundle branch block and right ventricular hypertrophy may obscure the electrocardiographic manifestations of left ventricular hypertrophy with or without an incomplete left bundle branch block.

Acknowledgement is made to Miss Mary L. Blazevich and Mrs. June J. Abeln for their technical assistance.

REFERENCES

1. Lenègre, J.: Contribution de l'étude des blocs de branche comportant notamment les confrontations électriques et histologiques. Paris, 1958, J. B. Baillière et Fils.
2. Lev, M.: The anatomic basis for disturbances in conduction and cardiac arrhythmias. Prog. Cardiovas. Dis. 2:360, 1960.
3. Lev, M.: The conduction system. *In* Gould: Pathology of the heart, ed. 2, Springfield, Ill., 1960, Charles C Thomas, Publisher, p. 137.
4. Lev, M., and Unger, P. N.: The pathology of the conduction system in acquired heart disease. I. Severe atrioventricular block. A.M.A. Arch. Path. 60:502, 1955.

Unger P N Lesser M E Kugel V H and Lev M The concept of masquerading bundle-branch block an electrocardiographic pathologic correlation Circulation 1 .397 19 8
6 Wilson F N Rosenbaum F F and Johnston F D Interpretation of the ventricular complex of the electrocardiogram Advances Int Med 2 1 1947
7 Milnor W R Electrocardiogram and vectorcardiogram in right ventricular hypertrophy and right bundle branch block Circulation 16 348 19
8 Lepeschkin E Modern electrocardiography Vol 1 The P-Q-R S-T U complex, Baltimore 1951 Williams & Wilkins Company
9 Criteria Committee of the New York Heart Association Inc Harold E B Pardee Chairman Nomenclature and criteria for diagnosis of disease of the heart and blood vessels ed 5 New York, 1953
10 Lev M and McMillan J B A semiquantitative histopathologic method for the study of the entire heart for clinical and electrocardiographic correlations Am. Heart J 58 140 19 9
11 Wilson F N and Herrmann G R An experimental study of incomplete bundle branch block and the refractory period of the heart of the dog Heart 8.229 1921
12 Rosenman R H Pick A and Katz L N The electrocardiographic patterns and the localization of intraventricular conduction defects Am Heart J 40 845 1950
13 Bisteni A., Sodi Pallares D Medrano G A and Pileggi F A new approach for the recognition of ventricular premature beats Am J Cardiol 5.358 1960
14 Erickson F E and Lev M Aging changes in the human atrioventricular node bundle and bundle branches *J Gerontol* 7 1952
15 Mahaim I Les maladies organiques du faisceau de His-Tawara Les syndromes coronaires L endocardite septale L infarctus septal Paris 1931 Masson et Cie
16 Yater W M Pathogenesis of bundle branch block Review of the literature report of sixteen cases with necropsy and of six cases with detailed histologic study of the conduction system Arch Int Med 6 1 1938
1 Kossmann C E Berger A R., Brumlik, J and Briller S A An analysis of causes of right axis deviation based partly on endocardial potentials of the hypertrophied right ventricle Am Heart J 35.309 1948

Comparative proximity and remoteness characteristics of conventional electrocardiographic leads

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The Einthoven limb leads have historically been treated as remote leads and the unipolar precordial leads as proximity leads. On the other hand, the direct relationship of the unipolar extremity leads to the Einthoven leads was initially emphasized. Later, in accordance with Wilson's electroposition concept, proximity characteristics were ascribed to these leads.

The introduction of the lead field into experimental electrocardiography has facilitated a more accurate expression of heart lead relationships. By definition, the lead field is the electrical field which is produced in the body when one unit of direct electrical current is caused to flow from the positive to the negative terminal of an electrocardiographic connection. Because of Helmholtz' principle of reciprocity, the gradient at any point within the field is identical to the lead vector at that point.

In order to assess the relative remoteness or proximateness of various electrocardiographic connections, we mapped lead field isopotentials upon the body surface of 7 human subjects and in the sagittal plane of a homogeneous torso model.

Methods and materials

In the portion of this study which was devoted to human subjects, we mapped the body surface traces of the bipolar lead field isopotentials by means of a previously described technique. In the analysis of Einthoven connections, each of the lead pathways was reciprocally energized with 1 milliampere square wave impulses of direct current. In the case of the augmented unipolar extremity leads, the technique was modified in such a way that each of two bipolar lead connections was simultaneously energized with 0.5 milliampere square wave impulses of direct current. The specific connections and directions of reciprocal energization which we employed are as follows: Lead aV_R energization = −0.5 Ma through Lead I pathway and −0.5 Ma through Lead II pathway; Lead aV_L energization = 0.5 Ma through Lead I pathway and −0.5 Ma through Lead III pathway; Lead aV_F energization = 0.5 Ma through Lead II and Lead III pathways each.

The electrocardiographic model employed in this study was constructed from

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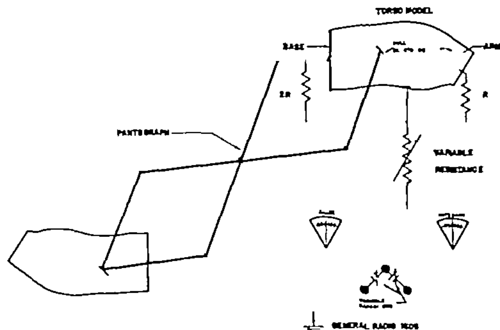


Fig. 1. Schematic representation of lead field mapping technique in torso model. The torso model (upper right) is in the left lateral recumbent position and filled with a suitable electrolyte. The lead connection illustrated consists of a midline precordial exploring electrode paired to the Wilson central terminal. The latter is formed from the base and left arm electrodes which have unequal resistors according to the principle of electrical images. The null or mapping electrode is located at an arbitrary site in the sagittal plane of the model. This site represents a null point when the lead connection has been balanced and a null reading obtained by the impedance comparator (lower right). The mapping electrode is then moved along a null (equipotential) line while the map is simultaneously transcribed from the model by a 1:1 pantograph (lower left). Further discussion in text.

a left half plaster-of-Paris mold of a human torso including the left arm. After the cast was waterproofed with several coats of an epoxy resin, the distal arm end and distal trunk portion were occluded with sealed-in aluminum plates and the neck end terminated in a fitted Lucite plate. With the model maintained in the left lateral recumbent position it was filled with ordinary tap water with a specific resistivity of 6,255 ohm-centimeter. It thus formed an open-faced electrolytic tank in which the surface of the fluid corresponded to the sagittal plane of the original subject. An electrode was located at any desired point about the boundary of the sagittal plane by applying silver conducting paint* to a semicircular area 1 cm. in diameter just beneath the surface of the electrolyte. The aluminum plates were coated with the same material to minimize voltaic effect.

*Walsco Silver Print No. 36, Walsco Electronics Manufacturing Co., Rockford, Ill.

The open construction of the model offers the particular advantage of making the interior, particularly the sagittal plane, readily accessible to an electrode probe. Thus it is a relatively simple matter to use a 1:1 pantograph, as shown schematically in Fig. 1, as an aid in the plotting of lead field isopotentials. The mapping procedure was further simplified by the use of a commercially available impedance comparator (see Appendix).

A total of 10 lead connections was studied. The 6 conventional extremity connections (Einthoven and augmented unipolar) were studied in 7 human subjects. Maps of all 6 limb connections were plotted in 4 cases; Einthoven leads only—in 1 case; augmented unipolar leads only—in 2 cases. The following 4 lead fields were mapped upon the sagittal plane of the model: midsternal V (near VE), midvertebral V (near VB), midsternal F (near CF), neck–lower extremities (Y). In a human subject the latter lead connection corresponds to

Table I Proximity and remoteness characteristics of conventional ECG leads

Lead	Grade	Subjects
I	Intermediate	
II	Semiremote	
III	Remote	5
[illegible]	Semiremote	6
[illegible]	Semiproximate	6
[illegible]	Remote	6
[illegible]	Proximate	Model
VB	Proximate	Model
CF	Semiproximate	Model
Y	Remo	Model

*Significant curvilinear distortion.

equally weighted resistors on the lower extremities and an equally weighted resistor on each side of the neck

Lead characteristics were determined by a comparison of the general form of the experimental lead fields (as extrapolated to the cardiac region) to ideal proximate and remote lead fields (Fig 2) On the basis of this qualitative visual comparison the various lead connections were graded as remote semiremote intermediate semiproximate and proximate Significant curvilinear distortion was also estimated

Results

In the human subject phase of the study no remarkable individual differences in the form of the field could be detected The subjects were normal young adults with body builds ranging from asthenic to thenic

The 10 leads which were studied are classified as to their relative proximity or remoteness in Table I Four representative lead fields are illustrated in Figs 3 4 5 and 6 These 4 fields demonstrate a progressive transformation from proximate to remote in the order of presentation Both the flow lines and isopotential lines are illustrated in the torso model fields (Figs 3 and 6) whereas only the isopotential lines are illustrated in the human subject field (Figs 4 and 5)

The first field (Fig 3) is that of a unipolar precordial lead and has been graded as proximate. This field was plotted in the torso model and approximates Lead V— since the lead connection was formed by pairing a mid-sternal exploring electrode at the level of the fourth intercostal space with the Wilson central terminal Although the field corresponds to the ideal proximate lead there is a slight asymmetrical curvilinear flaring of the flow lines Such flaring however should actually tend to exaggerate the proximity effect

The second field (Fig 4) is that of Lead aV_L as mapped upon a human subject and has been graded as semiproximate This lead is illustrated because it is more proximate than the other 5 conventional extremity leads but less than the degree evident in the unipolar precordial lead This decrease in proximity effect is not entirely a consequence of greater anatomic distance since it is also a result of the fact that the left shoulder represents an area electrode rather than a point electrode

The third field (Fig 5) is that of Lead aV_F as mapped upon a human subject and has been graded as remote It can be seen that the equipotential lines are relatively uniform in the cardiac region as in the case of the ideal remote lead and that curvilinear distortion is minimal Leads aV_F and III appear to be the most remote of the 6 conventional extremity leads

The fourth field (Fig 6) is that of a synthetic lead formed by connecting the neck with both lower extremities In a human subject this connection would correspond to equally weighted resistors on the lower extremities and an equally weighted re

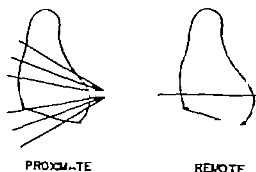


Fig 2 Ideal lead field Lead field flow lines in the case of an infinite homogeneous conducting medium when the electrode is near the heart (*proximate*) and when the electrode is withdrawn to a great distance (*remote* The flow lines are superimposed upon the cardiac silhouette Further discussion in text.

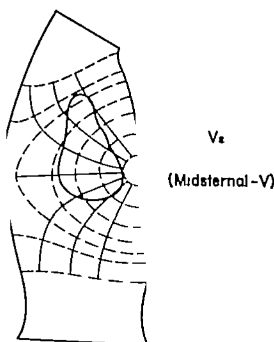


Fig. 3. Lead field of unipolar precordial lead which has been graded as proximate. Both the flow lines (*solid*) and isopotential lines (*dashed*) are illustrated and the cardiac silhouette has been superimposed. This field was plotted in the model.

sistor on each side of the neck. This field was mapped in the model and has been graded as remote. Although similar to Lead aV$_F$, there is even less curvilinear distortion. Because of its orientation and uniformity, this lead represents an ideal Y or vertical remote lead.

Discussion

The experimental lead fields were graded as to their degree of approximation to ideal proximate and remote lead fields. Such lead fields, as shown in Fig. 2, are in essence those that would occur in an infinite homogeneous conducting medium if the exploring electrode were located relatively near to the heart (in the case of the proximate lead) and if it were withdrawn to a large distance (in the case of the remote lead). In both cases the flow lines are rectilinear, but, as one might expect from their hypothetical origin, they appear to emanate from a point in the proximate lead and they are parallel in the remote lead. The situation is analogous to a chest roentgenogram with the film in contact with the patient's chest: if the tube is brought near to the chest, the tissues nearer the tube are exaggerated, whereas if the tube is withdrawn to a large distance, this proximity effect is not evident.

The proximate lead fulfills the requirements of the solid angle concept, whereas the remote lead may be analyzed according to the well-known lead vector principle. In terms of an equivalent multipolar cardiac generator, it may be further stated that the remote lead responds only to the dipolar components, whereas the proximate lead detects not only the dipolar but also the higher-order axially oriented components.

Although the flow lines are rectilinear in the case of the ideal leads, a certain element of curvilinear distortion occurred in all the conventional electrocardiographic leads. In certain instances, particularly the anterior and posterior unipolar chest leads, there was a symmetrical flaring of the flow lines through the cardiac region—at least in the sagittal plane. Although this feature prevents strict conformity to the solid angle concept, it nevertheless tends to augment the proximity effect. In other instances, particularly in Leads I and CF, there was an asymmetric flaring or "pinching together" of the flow lines within the cardiac region. When of significant degree, such distortion militates against strict approximation to the two ideal fields. Although some distortion is

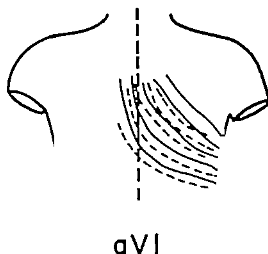


Fig. 4. Typical Lead aVL field map of a normal human subject which has been graded as semiproximate. Only the isopotential lines are illustrated, both anteriorly (*solid lines*) and posteriorly (*dashed lines*). Interval between isopotential lines is 2.0 mv.

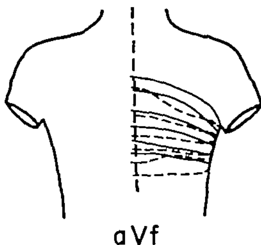


Fig 5 Typical Lead V field map which has been graded as remote Same subject as in Fig 4 Only the isopotential lines are illustrated as in Fig 4 Interval between isopotential lines is 1 5 mv

present in the conventional leads it is to be emphasized that both types of ideal leads may also be designed in the case of the human subject—at least in principle

There are certain features of the representative fields (Figs 3 6) and the classification (Table I) which have theoretical significance and thus appear worthy of further emphasis

I As already noted some curvilinear distortion is inherent in all the conventional electrocardiographic leads and thus they are not ideal in a strict sense However with two exceptions such distortion is slight and therefore the majority tend to approach the ideal

II Although in general the 6 extremity leads are relatively remote in comparison to the 2 unipolar chest leads some of them nevertheless exhibit considerable deviation from the ideal remote lead Thus whereas 4 of the connections were graded as remote or semiremote Lead I was graded as intermediate and Lead aV_L as semiproximate

A Leads aV_R and aV_F are relatively remote which is incompatible with the requirements of the electroposition concept

B Leads aV_F and III best approach the ideal remote lead However the synthetic neck–lower extremity connection appears superior to aV_F as a remote Y lead

C The left shoulder connection introduces greater proximateness manifest especially in Leads aV_L and I This feature undoubtedly contributes to the configuration and variation of the Burger triangle This represents a confirmation of Frank s studies in which the importance of the left arm attachment in the production of dipole location errors was emphasized [6]

III Both unipolar chest leads (V VB) studied are proximate and this effect is actually somewhat exaggerated because of symmetrical curvilinear flaring

IV Significant asymmetrical curvilinear distortion was noted in Leads I and CF_1 Therefore these leads possess more complicated characteristics—with neither solid angle nor lead vector analysis being strictly applicable

Although certainly informative the studies which form the basis of this report are admittedly crude The results are descriptive rather than quantitative In the studies performed upon human subjects it was necessary to perform the mapping upon the body surface with extrapolation to the interior cardiac region whereas during the torso model phase the mapping was limited to a single plane

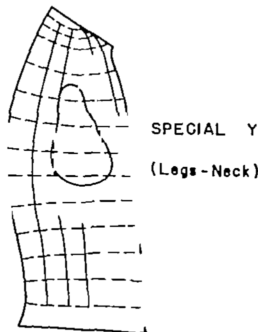


Fig 6 Lead field of the neck–lower extremity connection which has been graded as remote Both the flow lines (solid) and equipotential lines (dashed) are illustrated and the cardiac silhouette has been superimposed This field was plotted in the

However, with recent proposals concerning the application of equivalent multipoles to electrocardiographic analysis,[8] and with the more recent introduction of the lead tensor concept,[1] it is possible to perform a more advanced type of experimental analysis. In essence, it appears quite likely that a technique can be developed which consists of constructing a homogeneous torso model patterned after a given subject and then resolving numerous lead fields into their spherical harmonic components. It should then be possible to compute the derived equivalent multipolar components from the corresponding electrocardiograms recorded from the original human subject. The number of leads required to determine the equivalent cardiac generator through the nth order multipole is $n(n + 2)$. Therefore, in the event that an equivalent dipole + quadripole should be found adequate for representation of the human heart, it might be concluded that routine clinical electrocardiograms, which consist of 8 independent leads, contain all the diagnostic information that can be obtained from body surface electrocardiography. Preliminary results from a study of 8 lead cancellation, which is now in progress in this laboratory, indicate that multipolar representation through only the quadripole term may suffice for clinical purposes.

Hopefully, then, detailed lead field analysis may help to answer a number of important and interesting questions in electrocardiography.

Summary

1. The proximity and remoteness characteristics of 10 conventional lead connections were estimated by a comparison of experimental lead fields with ideal proximate and remote lead fields.

2. The experimental lead fields were determined by mapping the isopotential function upon the body surface of 7 human subjects and in the sagittal plane of a homogeneous torso model. A simplified mapping technique in electrolytic models is introduced and described.

3. Certain theoretical implications of the various lead characteristics are discussed.

4. Some of the limitations of the present study are noted, and the possibility of performing a more advanced type of experimental analysis in the future is briefly considered.

Appendix

I. Impedance comparator technique. The procedure of lead field mapping in electrolytic tank models is greatly simplified by the use of a commercially available impedance comparator* which gives a null reading when connected to two identical electrical impedances. The device operates at decade steps of frequency from 100 to 100,000 cycles per second, inclusive; at maximum sensitivity the impedance difference indicator covers a range of ± 0.3 per cent, and the phase angle difference indicator a range of ± 0.003 radians.† A frequency of 1,000 cycles per second was utilized in the present study.

The equipment employed in the torso model study is shown schematically in Fig. 1. The external resistances of the lead connections were sufficiently large to minimize alterations in the field due to possible variations in internal resistance. With the electrode probe at any arbitrary location immediately beneath the surface of the electrolyte, a null reading was obtained by balancing the external impedances. With this balance maintained, the probe was then moved along the null pathway, and in this manner it traced an equipotential line. As illustrated in Fig. 1, a 1:1 pantograph served as an aid in the mapping process. The procedure proved to be quite rapid, with slightly less than 1 hour generally being required to map the isopotentials of a single lead connection.

II. Electrical images. The electrocardiographic model was a left half model of a human torso, and the lead field mapping was performed in the sagittal plane. According to the principle of electrical images, lead field mapping is limited to configurations which are symmetrical with respect to the sagittal plane. For this reason, any torso surface electrode which is not applied to the midline is electrically equivalent to two equally weighted electrodes—the actual one together with an electrical

*General Radio Impedance Comparator Type 1605-A, General Radio Company, Cambridge, Mass.

†A later model is specified [illegible]

image which is mirrored by the sagittal plane

The Wilson central terminal in the model consisted of the base and left arm electrodes united to a common terminal. Although the base electrode is not identical to a left leg electrode, it can nevertheless be considered a very good approximation. Because of the principle of electrical images, the left arm electrode was provided with twice the weight of the base electrode. Thus the Wilson central terminal was equivalent to 3 equally weighted electrodes: the base, the left arm, and the mirror image of the left arm (i.e., the right arm).

REFERENCES

1. Wilson, F. N., MacLeod, A. G., and Barker, P. S.: The potential variations produced by the heart beat at the apices of Einthoven's triangle, Am. Heart J. 7:207, 1931.
2. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H. H., Cotrim, N., Menezes de Oliveira, R., Scarsi, R., and Barker, P. S.: The precordial electrocardiogram, Am. Heart J. 27:19, 1944.
3. Brody, D. A., and Romans, W. E.: A model which demonstrates the quantitative relationship between the electrical forces of the heart and the extremity lead, Am. Heart J. 45:263, 1953.
4. McFee, R., and Johnston, F. D.: Electrocardiographic lead. I. Introduction. II. Analysis. III. Synthesis, Circulation 8:554, 1953; 9:255 and 868, 1954.
5. Brody, D. A., Erb, B. D., and Romans, W. E.: The approximate determination of lead vectors and the Burger triangle in normal human subjects, Am. Heart J. 1:211, 1956.
6. Frank, E.: Absolute quantitative comparison of instantaneous QRS equipotentials on a homogeneous torso model, Circulation Res. 3:243, 1955.
7. Yeh, G. C. K., and Martinek, J.: Comparison of surface potentials due to several singularity representations of the human heart, Bull. Math. Biophysics 19:293, 1957.
8. Yeh, G. C. K., and Martinek, J.: Multipole representation of an eccentric dipole and an eccentric double layer, Bull. Math. Biophysics 21:33, 1959.
9. Geselowitz, D. B.: Multipole representation for an equivalent cardiac generator, Proc. Inst. Radio Engineers 48:75, 1960.
10. Brody, D. A., Bradshaw, J. C., and Evans, J. W.: The elements of an electrocardiographic lead tensor theory, Bull. Math. Biophysics (In press.)

Effects of intravenous lanatoside-C upon cardiodynamics in patients with mitral stenosis and regular sinus rhythm

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Previous studies have shown that the most consistent effects of digitalis preparations are increases in stroke volume and cardiac output, but only in subjects with myocardial failure. Changes in pressure in the lesser circulation and cardiac chambers vary according to the type of heart failure existing when the drug is administered. In patients with left ventricular failure digitalis produces decreases in pulmonary arterial pressures but no change in right ventricular end diastolic pressure. In patients with right ventricular failure digitalis usually causes a reduction in right ventricular end-diastolic pressure. When pulmonary hypertension due to a restricted pulmonary vascular bed is the cause of right heart failure, the increased cardiac output is frequently accompanied by an increase in pulmonary arterial systolic pressure. Davis, Howell, and Hyatt[7] have demonstrated in dogs that when right heart failure is produced by constriction of the pulmonary artery, the increase in cardiac output and decrease in diastolic pressures of the right heart after acute administration of digoxin are associated with a rise in right ventricular systolic pressure. In combined ventricular failure, pulmonary arterial pressures may show variable changes depending upon several factors, notably the initial pulmonary arterial pressures, the level to which stroke output increases, and the relative degrees of improvement in right and left ventricular functions.

It would be of interest to extend such studies to include the effects of digitalis preparations in patients who have obstruction to the passage of blood from the lungs but behind the left ventricle, as in isolated mitral stenosis. Work has been done in patients with this valvular lesion, but the results in many may have been obscured by coexisting defects such as mitral regurgitation, aortic stenosis, aortic insufficiency, and degenerative heart disease.[1,10,12] In the latter conditions left ventricular function may be impaired. Under such circumstances it would be difficult to evaluate changes in cardiodynamics after administration of digitalis, since the effects of myocardial and mechanical factors may not be readily separable. Studies have also been performed in subjects with mitral stenosis and coexisting atrial fibrillation.[1,13,14] It is well established that digitalis increases vagotonia, thereby decreasing conduction through the bundle of His and increasing

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the refractory period of the A V node and also acts directly on the A V node to inhibit conduction These effects are most prominent in atrial fibrillation resulting in an appreciable decrease in ventricular rate In subjects with mitral stenosis this increase in diastolic time would allow greater emptying of the left atrium and a reduction in the rate of flow across the stenotic valve Central vascular pressures behind the mitral valve may then decline to variable degrees[14] Again circulatory effects of the drug may be influenced by both the arrhythmia per se and the valvular stenosis

It was considered therefore that a review of the effects of these drugs in patients with isolated mitral stenosis and regular sinus rhythm would be valuable A study of patients with abnormal cardiodynamics due to a simple anatomic abnormality in whom the number of variables are minimal would allow for a more definitive evaluation of the effects of a drug on the circulatory system In this case mechanical hindrances to the passage of blood exist primarily at the mitral valve and secondarily in the pulmonary vascular bed The only ventricle whose function may be impaired is the right ventricle

Materials and methods

Seven female patients with mitral stenosis and regular sinus rhythm are the subjects of this study (Table I) They ranged in age from 17 to 48 years The past histories of 4 patients (Cases 2 4 7) included bouts of rheumatic fever in 1 of them (Case 2) one episode occurred 7 months previously but lasted only 2 to 3 weeks All subjects complained of effort dyspnea In 4 patients (Cases 3 4 6 7) dyspnea began 8 to 15 years ago and became increasingly severe during the past 1 to 2 years In 3 subjects (Cases 1 2 5) effort dyspnea of mild to moderate degrees occurred 1 7 and 24 months respectively before the present studies In 6 patients (Cases 2 7) orthopnea and bouts of nocturnal dyspnea were present for 7 months to 5 years In 3 patients (Cases 2 5 7) slight ankle edema occurred 1 to 2 years previously but disappeared after mercurial diuretic therapy In another patient (Case 4) ankle edema began 4 years ago and despite diuretic therapy progressed in extent and severity Physical examinations chest x ray films and electrocardiograms gave the following pertinent findings murmurs characteristic of mitral stenosis (Cases 1 7) soft early systolic apical murmur (Case 5) murmurs suggesting tricuspid regurgitation (Cases 4 7) peripheral edema (ankle sacral) (Case 4) ascites (Case 4) distended neck veins (Cases 4 and 7) hepatomegaly (Cases 4 and 5) enlarged pulmonary arterial segments (slight in Cases 2 and 3 moderate in Cases 1 6 and 7 marked in Cases 4 and 5) accentuation of peripheral pulmonary vascular markings (Cases 1 7) left atrial enlargement (slight in Case 2 moderate in Cases 1 3 5 6 7 marked in Case 4) right ventricular hypertrophy and enlargement (moderate in Cases 1 3 6 and 7 marked in Cases 4 and 5) right atrial enlargement (Cases 4 5 and 7)

Body temperatures and acute phase reactants were normal in all subjects Restriction of dietary salt was maintained in Cases 1 and 4 to 7 Several patients (Cases 4 7) had received mercurial injections during their previous illnesses In Cases 1 4 5 and 7 digitalis therapy had been maintained in the past however no patient received this therapy for at least 3 weeks prior to these studies

The presence of severe mitral stenosis (mitral valve area less than 1 0 cm) was later confirmed by surgical exploration in 3 patients (Cases 3 5 6) In 1 patient (Case 4) mitral commissurotomy (valve area less than 1 0 cm) had been performed 3 years prior to the present study However there was no change in the clinical state and it was assumed that severe mitral stenosis persisted Two patients (Cases 1 7) refused to undergo operation In 1 patient (Case 2) physiologic studies (vide infra) suggested that the mitral stenosis was mild operation therefore was not recommended

The patients were hospitalized and were semiambulatory or restricted to bed according to their functional capacities They were observed for 10 to 14 days during which time routine clinical observations were made and pertinent laboratory data obtained

Physiologic studies of cardiovascular hemodynamics by the standard technique of right heart catheterization were then per

formed (Tables IIA and IIB) The patients were in the recumbent positions and were not given premedication Duplicate measurement of cardiac output (direct Fick) were made in the resting state Oxygen consumption was obtained from analysis of expired air collected in a Tissot spirometer during 3 minutes of quiet breathing Samples of blood were obtained from the pulmonary and brachial arteries during the time of collection of expired air and were analyzed by the method of Van Slyke and Neill Multiple pressures were obtained with the use of Statham strain gauge transducers and recorded on a multichannel oscillographic photographic recorder Mean pressures were obtained by electrical integration of the pressure pulses The point of zero reference for measurement of intracardiac pressures was taken at 5 cm below the angle of Louis Total pulmonary vascular pulmonary arteriolar and total peripheral arterial resistances were calculated according to standard formulae (Poiseuille) Resistance is expressed as dynes sec cm^{-5} by the use of conversion factors † Since measurements of flow pressure and resistance did not vary significantly during the control periods only average values are tabulated (Tables IIA and IIB)

Lanatoside C 1 2 to 1 4 mg was then injected directly into the pulmonary artery through the catheter over a period of 2 to 3 minutes Pressures were measured at frequent intervals during the next 120 minutes Cardiac outputs (direct Fick) were determined at least twice in all but 1 case (determined once at 90 minutes in Case 2) from 30 to 90 minutes after administration of the drug Vascular resistances were calculated as described above For the sake of brevity only those parameters of cardiovascular dynamics which were measured at or closest to 10 30 60 and 90 minutes after administration of the drug are tabulated (Tables IIA and IIB) Because the data obtained after 90 minutes were similar to those obtained at 90 minutes they are omitted from the tabulation Other effects of the drug which may have occurred are described in the text

Changes in cardiovascular hemodynamics as a result of administration of the drug were evaluated in terms of statistical probabilities In order to determine whether these changes may have been due to chance variations or to the action of an introduced variable (lanatoside C in this study) an analysis was made of 29 consecutive right heart catheterizations performed in this laboratory in adults with various types of heart disease and with varying degrees of congestive failure In each of these studies at least 2 control determinations of resting cardiac output (direct Fick) multiple measurements of pressure and calculations of resistance were performed at intervals of ?2 to 143 minutes (average 41 minutes) while the patients states were considered to be constant Chance or expected variations in terms of 95 per cent confidence limits (2 standard deviations from the mean variation) were established on this basis for the various measures of cardiovascular hemodynamics A wide range of abnormalities in cardiodynamics was present in this control group as would be expected in any series of patients with heart disease and congestive failure It was thought therefore that greater reliability in an evaluation of the results would exist if these confidence limits were expressed in terms of percentage variations rather than changes in absolute values Two exceptions are pulmonary wedge and right ventricular end-diastolic pressures These parameters are expressed in terms of absolute changes because only minimal variations usually occur during a resting state and because small variations in their usually low numerical values frequently result in inordinately high percentage changes

Changes in cardiovascular dynamics in the present series of 7 patients who received lanatoside-C were then evaluated in terms of statistical significance at the 5 per cent level Changes that were considered to be statistically significant are appropriately indicated in Tables IIA and IIB and in the discussion of the results

Results

Control data (Tables IIA and IIB) Pulmonary hypertension was present in 6 of the 7 patients It was mild in 2 patients (Cases 1 3) moderate in 2 (Cases 5 6) and moderate to severe in 2 (Cases 4 7)

*Scholander gas analyzer

†1,332 = conversion factor from mm. Hg to dynes/cm.$^{-2}$

Table I Clinical status of patients at time of physiologic studies

Case	F C	Dyspnea	Orthopnea	Neck vein distention (Cm H₂O)	Liver size	Peripheral edema	Pulmonary vascular congestion (X-ray)	Cardiac chamber enlargement	Electrocardiogram	Previous therapy
1 Female Age 17 yr	II	Moderate	None	None	Normal	None	Moderate	LA—moderate RV—moderate	Atrial hypertrophy RVH	Low salt diet (3.0-4.0 Gm daily)
2 Female Age 29 yr	II	Mild	2 pillow	None	Normal	None	Slight	LA—slight	Atrial hypertrophy RAD	None
3 Female Age 29 yr	II	Moderate	2 pillow	None	Normal	None	Slight	LA—moderate	Normal	None
4 Female Age 32 yr	IV	Severe	3 pillow	90	5	Marked	Marked	LA—marked LV—marked RA—marked	Atrial hypertrophy RVH	Salt free diet frequent mercurial injections
5 Female Age 33 yr	III	Moderate	pillow	None	1	None	Moderate	LA—moderate RV—marked RA—moderate	Atrial hypertrophy RVH	Salt free diet frequent mercurial injections
6 Female Age 49 yr	III	Moderate	3 pillow	None	Normal	None	Moderate	LA—moderate RV—moderate	Atrial hypertrophy RVH	Salt free diet occasional mercurial injections
7 Female Age 19 yr	II	Moderate	2 pillow	45	Normal	None	Moderate	LA—moderate RV—moderate RA—moderate	Atrial hypertrophy RVH	Low salt diet (3.0-4.0 Gm daily) occasional mercurial injection

F C Functional classification (New York Heart Association)
Severe if at rest [illegible] moderate if during slight effort and slight if only during moderate effort
[illegible] below right costal angle
Marked [illegible] moderate [illegible] slight if involving ankles
LA Left atrium RV Right ventricle RA Right atrium RVH Right ventricular hypertrophy RAD Right axis deviation

Table IIA Cardiovascular hemodynamics before and after the administration of lanatoside C

Case	Lanatoside C (mg)	T	Heart rate (beats/min)	Oxygen consumption (c c /min /M)	A V O_2 difference (c c %)	Cardiac index (L /min /M)	Stroke volume (c c /beat)	Systemic arterial O_2 saturation (%)
1		Control	68	128	5 3	2 40	50	94
		10 min	62	—	—	—	—	—
	1 2	30 min	60*	—	—	—	—	—
		60 min	60*	148*	4 7	3 15	74	91
		90 min	65	142	4 9	2 90	63	90
2		Control	87	93	6 0	1 55	29	95
		10 min	80	—	—	—	—	—
	1 4	30 min	90	—	—	—	—	—
		60 min	75	—	4 9	—	—	94
		90 min	75*	84	6 0	1 40	31	94
3		Control	90	95	4 9	1 94	33	96
		10 min	75	—	—	—	—	—
	1 4	30 min	72	101	4 7	2 15	43	96
		60 min	70	101	4 9	2 06	47	95
		90 min	67	93	5 0	1 86	44	94
4		Control	95	137	10 1	1 35	19	89
		10 min	90	—	—	—	—	—
	1 2	30 min	88	—	—	—	—	—
		60 min	86	151	9 2	1 64	26	92
		90 min	90	152	9 3	1 64	25	92
5		Control	100	122	5 7	2 14	27	89
		10 min	83	—	—	—	—	—
	1 4	30 min	60	120	4 8	2 50	53	91
		60 min	73	138	5 0	2 76	49	91
		90 min	68	—	—	—	—	91
6		Control	76	138	5 6	2 46	60	93
		10 min	60*	—	—	—	—	—
	1 2	30 min	58*	—	—	—	—	—
		60 min	70	154	5 2	3 00	80*	91
		90 min	60*	138	5 0	2 76	86	94
7		Control	95	125	6 0	2 08	37	94
		10 min	80	—	—	—	—	—
	1 4	30 min	80	117	5 5	2 13	45	96
		60 min	93	114	5 6	2 04	37	96
		90 min	90	112	6 0	1 87	35	96

Under T Control denotes the period prior to the administration of lanatoside C (average values tabulated) This is followed by the periods 10 30 60 and 90 minutes after administration of the drug The tabulated data are the means ... these periods

*Denotes those values which statistically significantly differ (> 2 standard deviations) from control values

Pulmonary wedge pressures were measured during the control period in 5 patients they were elevated in all but 1 of them (Case 2) Right ventricular end diastolic pressures were normal in 3 patients (Cases 1 2 6) slightly elevated in 3 (Cases 3 5 7) and markedly elevated in 1 (Case 4) Systemic arterial pressures were normal in each subject

Cardiac outputs were low in all 7 patients Arterial mixed venous oxygen differences were elevated in all but 1 patient (Case 3) In 2 patients (Cases 4 5) systemic arterial oxygen saturations were slightly diminished

Total peripheral resistances were moderately elevated in all subjects Total pulmonary vascular resistances were elevated in all patients slightly in 2 (Cases

1 2) moderately in 2 (Cases 3 4) considerably in 3 (Cases 4 6) Pulmonary arteriolar resistances calculated during the control periods in 5 patients were found to be slightly abnormal in 3 (Cases 1 3) and moderately elevated in 2 (Cases 4 5)

Cardiovascular dynamics after the administration of lanatoside C (*Tables IIA and IIB*) In 2 (Cases 2 6) of the 7 subjects lanatoside C did not affect cardiovascular dynamics to any important degree Significant reductions in heart rates occurred

Table IIB Cardiovascular hemodynamics before and after the administration of lanatoside C

Case	T	Pressure (mm Hg)								Resistance (dynes/sec /cm⁻⁵)		
		Peripheral artery			Pulmonary artery			Pulmonary wedge	Right ventricle (D†)	Total systemic	Total pulmonary vascular	Pulmonary arteriole
		S	D	M	S	D	M	M				
1	Control	120	69	86	41	19	25	15	1	2 040	575	210
	10 min	—	—	—	39	19	26	—	2	—	—	—
	30 min	116	63	84	47	21	29	—	2	—	—	—
	60 min	125	68	84	50	19	30	17	1	1 510	570	195
	90 min	123	68	85	48	20	30	17	0	1 660	605	272
2	Control	110	61	77	20	8	12	7	3	2 430	3 0	150
	10 min	120	59	79	18	6	10	—	1	—	—	—
	30 min	116	57	82	20	8	11	—	1	—	—	—
	60 min	116	51	68	20	7	11	—	3	—	—	—
	90 min	102	55	69	20	7	11	5	3	2 410	385	210
3	Control	107	61	77	37	20	27	21	6	2 000	730	220
	10 min	116	69	85	41	18	22	—	7	—	—	—
	30 min	105	66	80	37	17	22	—	5	1 880	570	—
	60 min	101	56	75	33	14	1	15	4	1 840	520	290
	90 min	10	57	74	36	14	21	15	8	2 010	680	270
4	Control	93	66	73	96	40	59	48	22	3 250	2 660	665
	10 min	103	73	80	114	55	59	—	24	—	—	—
	30 min	—	—	—	114	40	57	—	23	—	—	—
	60 min	100	62	72	120	41	61	52	21	2 590	2 190	325
	90 min	170	0	80	120	42	67	—	18	2 840	2 410	—
5	Control	92	61	73	74	3	40	30	8	2 120	1 480	570
	10 min	123	68	86	63	29	41	—	2	—	—	—
	30 min	118	59	79	90	20	30	16	3	1 980	750	380
	60 min	112	56	78	64	22	33	—	1	1 760	00	—
	90 min	112	56	74	60	20	32	14	0	—	—	—
6	Control	134	77	94	75	23	42	—	5	1 640	734	—
	10 min	158	84	109*	65	17	34	—	4	—	—	—
	30 min	150	80	105	83		40	—	3	—	—	—
	60 min	146	77	100	78	23	40	17	4	1 340	570	330
	90 min	132	6	84	78	22	39	18	3	1 350	610	330
7	Control	136	78	104	125	41	74	—	6	2 400	1 00	—
	10 min	153	71	104	109	28	33	—	5	—	—	—
	30 min	121	58	82	110	37	6	—	5	2 300	1 380	—
	60 min	123	5	103	111	39	58	—	2	2 390	1 350	—
	90 min	124	71	90	125	38	63	—	2	2 280	1 600	—

T Same as in Table IIA
Denotes those values which are statistically significantly different (> 2 standard deviations) from control values
† End-diastolic.

60 and 10 minutes after administration of the dru and continued for the remainder of the studies In Case 6 stroke volumes rose

In the other 5 patients (Cases 1 3 5 7) important changes in cardiovascular hemodynamics occurred after administration of the drug In Cases 3 5 7 pulmonary arterial diastolic and mean pressures decreased significantly In Case 7 this response was transient at 10 and 60 minutes In Cases 3 and 5 these changes occurred at 60 and 30 minutes respectively and continued for the remainder of the study In 2 patients (Cases 3 and 5) pulmonary wedge pressures were measured before and after administration of the drug significant reductions were noted concomitant with the changes in pulmonary arterial pressures In Case 5 a transient decrease in pulmonary arterial systolic pressure occurred at 30 minutes In each of these 3 patients significant decreases in heart rates occurred 10 minutes after administration of the drug In 2 of them (Cases 3 and 5) the changes in heart rate persisted in the other (Case 7) the heart rate returned to control levels at 60 minutes Stroke volumes increased significantly in Cases 3 and 5 Only in the latter case did stroke volume increase enough to effect a significant increase in cardiac output In these 3 subjects control right ventricular end diastolic pressures were elevated In Case 3 no changes occurred after administration of the drug In Cases 5 and 7 right ventricular diastolic pressure decreased significantly and to normal at 10 and 60 minutes respectively and remained at these levels or lower for the duration of the studies Pulmonary vascular resistances did not change except in 1 subject (Case 5) in whom there was a moderate reduction in total pulmonary vascular resistance

In the other 2 (Cases 1 4) of the 5 patients in whom important hemodynamic changes occurred after therapy with lanatoside C there were significant increases in pulmonary arterial systolic pressures but no changes in pulmonary arterial diastolic and mean pressures In 1 subject (Case 4) this increase occurred at 10 minutes and remained at that level for the rest of the study This was associated with significant increases in stroke volumes and at 90 minutes with a definite reduction in right ventricular end diastolic pressure (The latter was abnormal during the control period) Heart rate did not change Cardiac output increased somewhat but not to a significant degree In the other patient (Case 1) pulmonary arterial systolic pressure rose transiently at 60 minutes This was associated with significant increases in stroke output cardiac output and oxygen consumption It is not entirely certain that these effects were due to the glycoside They may have been a consequence of a change in metabolic state as indicated by the significant increase in oxygen consumption

Additional information Systemic arterial pressures increased in some subjects (Cases 4 7) In 1 subject (Case 5) systolic pressure increased 10 minutes after administration of the drug and continued to be elevated for the remainder of the study In the other 3 subjects the increases were transient and inconstant and bore no relationship to changes in other parameters of cardiovascular function

Systemic arterial oxygen saturations did not change after drug therapy

There were no changes in signs or symptoms as related to the cardiovascular system after administration of lanatoside C In Case 2 slight nausea occurred after 23 minutes and in Case 7 periodic first degree A V block and intermittent shifting atrial pacemaker occurred after 30 minutes

Discussion

Changes in cardiodynamics after the administration of lanatoside C in the subjects of this study were variable However the data do indicate certain patterns the formation of which depend on the actions of the drug to a greater or lesser degree upon various components of the cardiovascular system and also upon the physiologic status of the patient at the time of the study

One pattern is illustrated by the results in Case 4 In this subject there was an early rise in pulmonary arterial systolic pressure accompanied by an increase in stroke output and later by a decrease in right ventricular end-diastolic pressure Pulmonary arterial mean and diastolic pressures and pulmonary wedge pressure

did not change Cardiac output rose somewhat but not to a significant degree Heart rate did not change These changes are generally similar to those which follow the administration of cardiac glycosides in chronic cor pulmonale After drug therapy the decrease in filling pressure and presumably in residual blood volume of the right ventricle indicates better emptying of this chamber as a consequence of improvement in its function The increase in stroke output takes place in a pulmonary vascular bed from which the outflow is obstructed In chronic cor pulmonale the obstruction is at the pulmonary precapillary area whereas in mitral stenosis the obstruction is primarily at the mitral valve and secondarily at the pulmonary precapillary area (Pulmonary arteriolar resistance was markedly elevated in our case) An increase in flow through an area of increased resistance is accompanied by a rise in pressure proximal to the obstruction This would explain the increases in pulmonary arterial systolic pressures in both conditions

Another pattern is illustrated by Cases 3 5 and 7 In this group of patients the most consistent changes in the lesser circulation after administration of the drug were declines in pulmonary arterial diastolic and mean pressures Various possibilities may be suggested to account for this occurrence A reduction in pulmonary arteriolar resistance may offer less obstruction to outflow from the right ventricle and thereby allow a reduction in the pressure head relative to this flow Pulmonary arterial systolic pressure should then decrease unless there is an appreciable increase in blood flow Blood flow did not increase significantly in 2 of these 3 subjects and pulmonary arterial systolic pressures did not show consistent changes In addition calculated pulmonary arteriolar resistances did not change (Cases 3 and 5)

Another factor which could have caused a reduction in pulmonary arterial pressures is dilatation of the pulmonary vascular bed It has been suggested that digitalis preparations may directly influence certain vascular beds such as to produce systemic venous pooling[8, 9] and to increase total peripheral arterial resistance [10] In the human subject with heart failure however such effects are relatively minor and are overshadowed by other cardiovascular changes There is no evidence to date that digitalis preparations cause a dilatation of the pulmonary vascular bed Although this possibility cannot be definitely eliminated from consideration the unlikelihood of its occurrence and the absence of supporting data in the literature suggest that its role i e a change in distensibility properties of the pulmonary vasculature in contributing to the changes noted in this study is negligible

A decrease in right ventricular stroke output may contribute to a decrease in pulmonary arterial pressure However this was not a factor in this study because stroke output did not fall in fact it increased in Cases 5 and 7

Decreases in pulmonary blood volumes (albeit not supported by direct measurements) could have been responsible for the declines in pulmonary diastolic and mean pressures as well as for the declines in pulmonary wedge pressures Other investigators have demonstrated that the relationship between pulmonary blood volume and pulmonary vascular pressures is dependent upon the volume elasticity properties of the pulmonary vasculature [11] The pressure volume curves of this vascular bed are characterized by upward convexities when pressure is plotted on the vertical axis Thus at normal levels of pulmonary blood volume and pulmonary pressures changes in volume produce minimal changes in pressure As volume increases progressively a point is reached at which pressure rises sharply At elevated levels of pressure small changes in volume may accomplish appreciable changes in pressure The presence of pulmonary arterial and venous hypertension in our subjects probably indicates that pulmonary blood volume was initially increased to some degree It then reasonably appears that since other factors (see above) were constant the changes in pressures after administration of the drug were due to changes in volumes

It would be important to know how reductions in pulmonary blood volumes could have been produced in these subjects (Cases 3 5 7) Since falls in right ventricular output did not occur improve-

ment in emptying of the left heart remains as the logical alternative The mode by which the latter may have been accomplished is somewhat speculative but the data do permit reasonable conclusions A positive inotropic effect of the digitalis preparation on a decompensated left ventricular myocardium is one possibility Other workers [illegible] have demonstrated improvements in cardiac output and in pulmonary arterial pressures after the administration of a cardiac glycoside to patients with left ventricular failure In human subjects without myocardial failure however these drugs do not influence pressures in the lesser circulation and either do not change or do cause a reduction in cardiac output [illegible] It would have been valuable in this respect to measure left ventricular end diastolic pressures in our subjects since this would have given more direct indications of the function of the left ventricle However it was considered that prolonged catheterization of the left heart would incur excessive risk Clinically at least there was no reason to suspect alteration in left ventricular function although the possibility of the histologic stigmas of rheumatic myocarditis always exist Certainly the size of the left ventricle was normal as demonstrated by clinical examination (Cases 1 7) and at operation (Cases 3 6) In addition in 2 *(Cases 3 and 7) of these 3 patients (Cases* 3 5 7) cardiac output did not change after drug therapy an occurrence which is unusual when digitalis is administered to subjects with bona fide left ventricular failure [1, 8, 11, 13]

A more likely mechanism for the improvement in the emptying of the left heart is the reduction in ventricular rates This occurred in each subject (Cases 3 5 7) in this group almost simultaneously with the changes in pulmonary arterial pressures The influence of ventricular rate per se upon lesser circulatory pressures in mitral stenosis is well known [5, 6, 7] The pressure gradient across the stenotic valve depends upon the flow across that valve In mitral stenosis this (diastolic) flow has the characteristics of a steady rate (rather than an accelerated rate in early diastole when the valves are normal) Thus the diastolic period becomes an important determinant of the amount of blood which can leave the lungs and left atrium per unit time Therefore by the simple mechanism of ventricular bradycardia due to drug action on vagal centers and directly on cardiac conduction tissue the period during which flow can occur across the stenotic mitral valve is increased permitting a greater emptying of pulmonary (and possibly left atrial) vascular beds a decrease in their blood volumes and thus falls in pressures behind the valve That the increases in stroke volumes in Cases 3 and 5 are secondary to this bradycardia rather than due to primary inotropic effects of the drug is suggested by the observations that (a) in Cases 3 and 7 cardiac outputs did not change (cardiac output usually increases concomitant with stroke output after digitalis therapy in myocardial failure as described above) and (b) in Case 7 stroke output did not change although ventricular rate decreased indicating that the latter may occur as a primary phenomenon

The influence of ventricular rate upon pulmonary arterial pressures is further emphasized in Case 7 Drug induced bradycardia occurred transiently at 10 and 30 minutes This was associated with reductions in pulmonary arterial mean and diastolic pressures (at 10 minutes) A return of heart rates to control levels at *60 and 90 minutes led to a restoration of* pulmonary pressures (at 90 minutes)

In these 3 subjects (Cases 3 5 7) right ventricular end-diastolic pressures were initially abnormal In 2 (Cases 5 7) lanatoside C improved the function of the right ventricle causing decreases in the filling pressures of the right heart to normal after 10 and 60 minutes respectively

A third pattern is represented by the other 3 cases (Cases 1 2 6) Significant reductions in ventricular rates occurred after administration of the drug but there were no other important changes in cardiodynamics which could be attributed to the cardiac glycoside It is not clear why bradycardia may permit decreases in pulmonary pressures in some cases and not in others In 1 case (Case 6) right ventricular end-diastolic pressure which was abnormal during the control period did not change Again no explanation is apparent

for the improvement in function of the right ventricle in some instances and not in others. Perhaps the inability of the myocardium to respond because of pathologic factors is of some importance.

Other workers[illegible] have demonstrated that cardiac glycosides may increase systemic arterial pressure by affecting peripheral resistance. In Cases 4 to 6 increases in systemic arterial pressures did occur but they were variable and followed no pattern nor did they have any definite relationship with the other changes in cardiodynamics described above. Peripheral resistances did not change (Cases 5, 6) or actually decreased (Case 4). It appears that the effects of digitalis on peripheral resistance are minor in human congestive heart failure and that the more important effects of this drug on cardiac function determine cardiodynamic events to a greater degree.

It appears therefore that the ultimate changes in cardiodynamics after the administration of digitalis in patients with mitral stenosis and regular rhythm depend upon the interaction of several factors. Improvement in right ventricular function results in increased output into a vascular bed from which outflow is obstructed and in which capacity may be restricted; right ventricular end-diastolic pressure tends to fall; cardiac output and stroke volume tend to rise and pulmonary arterial systolic pressure tends to rise. Drug-induced bradycardia with its attendant increase in diastolic time may permit greater emptying of the pulmonary vascular bed across the narrowed valve area, which in turn may accomplish reductions in pulmonary arterial diastolic and mean pressures. Stroke volume may rise as a phenomenon secondary to the bradycardia. Cardiac output increased only in 1 subject (Case 5) who had improvement in right ventricular function. In our subjects when both improvement in right ventricular function and bradycardia occurred at the same time the latter appeared to exert the dominant influence upon pulmonary vascular pressures. In some subjects right ventricular function may not improve and bradycardia may not influence central vascular pressures. The effect of the drug on peripheral resistance was unimportant.

In the present discussion the concept of improvement in right ventricular function has been applied in a general manner. The data do not indicate the primary site of action of the drug, whether on the myocardium as a positive inotropic effect or on a peripheral venous vascular bed to reduce venous return and thereby improve cardiac overstretch. The time relationships between cardiac output and pressures are not helpful because the former was not measured earlier than 30 minutes after administration of the drug.

The clinical application of digitalis in patients with mitral stenosis and regular sinus rhythm may offer some benefit although not so impressive as in patients with left ventricular decompensation. If a reduction in ventricular rate should occur, at least in the nonexercising state, a decrease in pulmonary blood volume and salutary falls in lesser circulatory pressures may result. If right ventricular failure exists the drug may improve the function of the right ventricle. It has been stated[illegible] that an increase in the output of the right ventricle (as the function of this chamber improves) into a pulmonary vascular bed from which the outflow is obstructed may raise the pulmonary capillary hydrostatic pressure and produce pulmonary edema. The necessary prerequisite for this effect on cardiac output is a decompensated right ventricle. The latter is usually associated with an appreciable elevation in pulmonary arteriolar resistance. In this study only 1 case (Case 4) illustrates this set of circumstances (in which the effects of increased flow upon pulmonary pressures were not overshadowed by bradycardia). In this subject pulmonary wedge pressure although markedly elevated initially did not rise further. The pressure which rose as flow increased was that behind the pulmonary precapillary bed (pulmonary systolic pressure).

Summary

This study is concerned with the acute effects of intravenous lanatoside C upon the cardiovascular dynamics of 7 female patients with mitral stenosis and regular sinus rhythm.

Control data revealed that pulmonary arterial hypertension of mild to severe degrees was present in 6 patients; pul-

nary wedge pressures were elevated in 4 of the 5 patients in whom they were measured cardiac outputs were depressed in all patients and right ventricular de compensation as indicated by an elevation in end diastolic pressure was present in 4 patients Pulmonary vascular resistances were elevated to variable degrees in all patients

The cardiodynamic responses to the administration of lanatoside C were dis tinguished by 3 patterns In one pattern improvement in right ventricular function (abnormal initially) resulted in an increased output into a vascular bed from which the outflow was obstructed Right ventricular end diastolic pressure fell cardiac output and stroke volume rose and pulmonary ar terial systolic pressure rose A second pattern demonstrated the salutary effects of brady cardia with its attendant increase in dias tolic time This permitted greater empty ing of the pulmonary vascular bed which in turn caused reductions in pulmonary arterial diastolic and mean pressures and pulmonary wedge pressure Stroke vol umes increased as phenomena secondary to the bradycardia Cardiac output in creased in that subject who had improve ment in right ventricular function When both improvement in right ventricular function and bradycardia occurred in the same subject the latter exerted the dom inant influence upon pulmonary vascular pressures The third pattern was character ized by an absence of hemodynamic changes after administration of lanatoside C

The possible benefits which the adminis tration of digitalis may exercise in pa tients with mitral stenosis and regular sinus rhythm are discussed

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REFERENCES

1 Harvey R M Ferrer M I Cathcart R T Richards D W J and Cournand A Some effects of digoxin upon the heart and circulation in man Digoxin in left ventricular failure Am J Med 7 439 1949
2 Ferrer M I Harvey R M Cathcart R T Webster C A Richards D W Jr and Cournand A Some effects of digoxin upon the heart and circulation in man Digoxin in chronic cor pulmonale Circulation 1 161 1950
3 Harvey R M Ferrer M I Cathcart R T and Alexander J K Some effects of digoxin on the heart and circulation in man Digoxin in enlarged heart not in clinical congestive failure Circulation 4 366 1951
4 Ferrer M I Conroy R J and Harvey R M Some effects of digoxin upon the heart and circulation in man Digoxin in combined (left and right) ventricular failure Circulation 21:372 1960
5 Stead E A Jr Warren J V and Brannon E S Effect of lanatoside C on the circulation of patients with congestive failure Arch Int Med 81:282 1948
6 Ahmed S Bayliss R I S Briscoe W A and McMichael J The action of ouabain (G-strophanthin) on the circulation in man and a comparison with digoxin Clin Sc 9:1 1950
7 Davis J O Howell D S and Hyatt R E Effects of acute and chronic digoxin administration in dogs with right sided congestive heart failure produced by pulmonary artery constriction Circulation Res 3:259 1955
8 McMichael J Cardiotonics and diuretics in human heart failure J Chron Dis 9 607 1959
9 Eichna L W Farber S J Berger A R Earle D P Rader B Pellegrino E Albert R F Alexander J D Taube H and Youngwirth S The interrelationships of the cardiovascular renal and electrolyte effects of intravenous digoxin in congestive heart failure J Clin Invest 30 1250 1951
10 Bricht H Ek J Eliasch H Thomasson B and Werkö L The effect of single *intravenous dose of Scillaren B on the pulmonary* circulation and renal function in patients with rheumatic heart disease Am Heart J 54 376 1957
11 Y P N Ny R E Jr Lovejoy F W Jr Macias J Dej Schreiner B F and Lux J J *Studies of pulmonary hypertension* Effects of acetylstrophanthidin on pulmonary circulation in patients with cardiac failure and mitral stenosis Am Heart J 54 235 1957
12 Gray F D J and Gray F G The effect of lanatoside C on the circulatory and ventilatory changes of chronic rheumatic heart disease with mitral stenosis Am Heart J 47 282 1954
13 Ferrer M I Harvey R M Cathcart R T Cournand A and Richards D W J Hemodynamic studies in rheumatic heart disease Circulation 6 688 1952
14 Hammond J and Whitaker W Effects of intravenous digoxin in uncontrolled auricular fibrillation Brit Heart J 19 3 1957
15 Bloomfield R A Rapoport B Milnor J P Long W K Mebane J G and Ellis L B Studies in mitral stenosis The effect of ouabain on the circulation in patients with pulmonary disability Arch Int Med 89 970 1952
16 Gorlin R Haynes F W Goodale W T Sawyer C G Dow J W and Dexter L Studies of the circulatory dynamics in mitral stenosis Altered dynamics at rest Am H art J 41:30 1951

17 Scholander P F Analyzer for accurate estimation of respiratory gases in one half cubic centimeter samples J Biol Chem 167:235 1947
18 Van Slyke D D and Neill J M The determination of gases in blood and other solutions by vacuum extraction and manometric measurement J Biol Chem 61 524 1924
19 Lewis B M Gorlin R Houssay H E J Haynes F W and Dexter L Clinical and physiological correlations in patients with mitral stenosis Am Heart J 43 2 1952
20 McMichael J Circulatory failure studied by means of venous catheterization I Advances in internal medicine New York 1947 Interscience Publishers Inc p 77
21 Ross J Jr Braunwald E and Waldhausen J A Studies on digitalis Extracardiac effects on venous return and on the capacity of the peripheral vascular bed J Clin Invest 39 937 1960
22 Ross J Jr Waldhausen J A and Braunwald E Studies on digitalis Direct effects on peripheral vascular resistance J Clin Invest 39 930 1960
23 Sarnoff S J Berglund E and Sarnoff L C Neurohemodynamics of pulmonary edema Estimated changes in pulmonary blood volume accompanying systemic vasoconstriction and vasodilatation J Appl Physiol 5:367 1953
24 Sarnoff S J and Berglund E Pressure volume characteristics and stress relaxation in the pulmonary vascular bed of the dog Am J Physiol 171 238 1952
25 Opdyke D F Duomarco J Dillon W H Schreiber H Little R C and Seely R D Study of simultaneous right and left atrial pressure pulses under normal and experimentally altered conditions Am J Physiol 154:258 1948
26 Wood P and Paulett J The effects of digitalis on the venous pressure Brit Heart J 11:83 1949
27 Gorlin R Sawyer C G Haynes F W Goodale W T and Dexter L Effects of exercise on circulatory dynamics in mitral stenosis Am Heart J 41 192 1951

Sinus arrhythmia in rheumatic fever

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One of the first descriptions of sinus arrhythmia was by Ludwig in 1847. In 1860 Einbrodt,[2] a pupil of Ludwig, suggested that the cause of sinus arrhythmia was an alteration in the tone of the cardio-inhibitory center. Brodie and Russell[3] agreed with Einbrodt, but Hooker[4] showed that this explanation was inadequate because they were able to produce reflex changes in the heart rate via the accelerator nerves after the vagi had been cut.

The stimulus which changes the tone of the cardio-regulatory centers is not known for certain. Among the theories advanced have been chemical changes in the blood, the Hering-Breuer reflex,[6] overflow of stimuli from the respiratory center,[7] stimuli from muscles of respiration,[8] and stimuli from rise of pressure in the right auricle *and great veins*.[9] *However, as Landtman*[11] says, "It is possible that several of these factors contribute."

In 1902 Mackenzie[12] separated sinus arrhythmia from other causes of irregular action of the heart and called it the "youthful type of irregularity." He noted that it *occurred especially between the years of 8* and 15. He pointed out that after rheumatic fever it was commonly taken to be a grave sign, but he had observed that the presence of sinus arrhythmia indicated the absence of heart involvement. He said that he had never seen sinus arrhythmia in acute rheumatic fever nor in progressive rheumatic heart disease, and that its presence in old valvular affections suggested that there was no active carditis.[13]

Parkinson and Hope Gosse[14] stated that the presence of sinus arrhythmia did not indicate that the heart had escaped involvement, recent or remote. McCrudden[15] observed that sinus arrhythmia *occurred in rheumatic fever but that its* absence carried a poor prognosis. Lumsden[16] said that severe sinus arrhythmia is sometimes caused by the rheumatic process. Lewis[7] commented that it is especially frequent in patients with rheumatic heart disease when they are taking digitalis. Wood[18] *stated that, although it is normal,* it may occur in any form of heart disease, and Myers[8] pointed out that it occurs in children with acute rheumatic carditis.

Nordenfelt[19] compared the degree of sinus arrhythmia in normal children with that in 126 sick children. He found that the values were similar in both groups, but unfortunately his group of sick children included children with endocarditis

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due to causes other than rheumatic fever such as respiratory infection with heart murmurs the group with disease was therefore not homogeneous Landtman[11] made a comprehensive study of the degree of sinus arrhythmia in a group of normal children and in a group with active rheumatic carditis and found less sinus arrhythmia in the group with disease

We felt that although adequate data were available on sinus arrhythmia in rheumatic carditis[11] it was worth while to collect further data on patients with initial attacks (with and without carditis) and on those with recurrences of rheumatic fever

Plan of study

Material Sinus arrhythmia was studied in two series of children The first group consisted of children with an acute initial attack of rheumatic fever these were studied on admission and on discharge The second group consisted of children admitted with a recurrent attack of rheumatic fever Our material was comprised of patients in the cooperative trial of ACTH cortisone and aspirin and those in a current therapeutic trial[17] All patients had been in the House of the Good Samaritan and the age limit was 17 years After the exclusion of patients in whom the P R interval varied or was prolonged those in whom the rhythm did not originate in the sinus node and those in whom electrocardiograms were not available there were 135 patients for the present study of whom 85 were suffering their initial attack A group of 93 children with normal hearts was used as controls[21] These were patients in the Children's Medical Center who had not had rheumatic fever and who were free of cardiac disorders and infection Their cardiovascular systems had been examined by a cardiologist and were found to be entirely normal Patients with an initial attack of rheumatic fever were divided into those without carditis (normal heart rheumatic group 27 patients) and those with carditis (carditis group 58 patients)

Carditis was considered to be present if any of the following conditions existed development of an organic apical systolic murmur or an aortic diastolic murmur under acceptable observation pericarditis revealed by a definite friction rub or by pericardial effusion or congestive failure Congestive failure was always accompanied by either of the other two conditions

Age and sex distribution are shown in Table I There was a greater proportion of children under 6 years of age in the control group than in any of the study groups and a greater proportion of children over 10 years of age in the normal heart group About one and one half times more boys were present in the control and normal heart groups whereas more girls were present in the carditis group The recurrence group is described later

Method We examined the electrocardiogram taken with three standard leads each usually comprising six complexes The maximum and minimum R R intervals were measured to the nearest 0 5 mm and the average of six R R intervals was measured The degree of sinus arrhythmia (frequency index) was then calculated using the method described by Schlomka and Reindell Thus the shortest R R interval was subtracted from the longest R R interval and the result was divided by the mean of six R R intervals and multiplied by 100 This method has been used because it takes into consideration the heart rate and because it expresses sinus arrhythmia quantitatively

Table I *Age and sex*

Group	*Age (years)*			*Total*	*Boys*	*Girls*
	2–5	6–10	11 17			
Control	25	49	19	93	56	37
Rheumatic fever						
Normal heart	0	1	12	27	17	10
Carditis	6	36	16	58	24	34

Table II Frequency index on admission

Group	*Number*	*Frequency index*	*Mean heart rate*
Control	93	22 3 ± 1 4	93
Rheumatic fever			
Normal heart	27	18 9 ± 3 0	96
Carditis	58	14 6 ± 2 0	116

Results

On admission Table II shows the average frequency index on admission The control and normal heart groups had similar frequency indices with means of 22 3 and 18 9 and average heart rates of 93 and 96 respectively The mean frequency index of 14 6 in the carditis group was however less and the difference between this and the figure for the control group was highly significant (p = < 01 > 001) The carditis group however had a higher average heart rate and Table III shows that in patients whose rates were less than 100 per minute the frequency indices were similar in all groups Table IV shows the frequency indices of patients whose heart rates were 100 per minute or more This showed that at these faster rates the frequency indices of both the normal heart and carditis groups were significantly lower than that of the control group (p = < 01 > 001)

On discharge The change in the frequency index by the time of discharge was next investigated (Table V) The normal heart group showed a significant decrease in the index as compared with that at the time of admission (p = < 05 > 02) but the difference in the frequency index of the carditis group between admission and discharge was not significant at the 5 per cent level Both groups showed very similar degrees of sinus arrhythmia at the time of discharge

Recurrences

The group of 50 children suffering recurrences has been analyzed separately The age and sex of these children are shown in Table VI They were older than those with an initial attack 70 per cent were more than 10 years of age as compared with 33 per cent of those having an initial attack Duration of disease before admission was difficult to determine because in some patients the onset was insidious but in general it was about 3 weeks longer than in those with an initial attack

Table VII shows the frequency index in the recurrence group at the time of admission Values for the carditis group on admission and on discharge are included in the table for comparison The difference in frequency indices between the two groups on admission was highly significant (p = < 001) but the difference between the recurrence group on admission and the carditis group on discharge was small and not significant (p = <0 1> 05) There was a similar small difference between the recurrence group on admission and the normal heart group on discharge

The recurrence group was divided into two groups on the basis of heart rate like the grouping for those with an initial attack and Table VIII shows the results At slow rates there was a highly significant decrease in sinus arrhythmia in the recurrence group as compared with findings in the control or normal heart or carditis groups on admission At the faster rates although the difference between the recurrence and carditis groups was less marked it was significant at about the 5 per cent level (p = < 05 > 02) and this in spite of the presence of an average faster heart rate in the carditis group

Discussion

Our results (Table II) suggest that sinus arrhythmia is significantly less marked in patients with an initial attack of rheumatic fever with carditis than in our controls There were differences between those patients with carditis and those without and between controls and those without carditis but these differences were not large The average heart rates in the control and normal heart groups were similar (93 and 96 respectively) but in the car

Table III Frequency index on admission in patients with heart rates under 100 per minute

Group	Number	Frequency index	Mean heart rate
Control	62	26 6 ± 1 7	82
Rheumatic fever			
Normal heart	15	28 8	81
Carditis	17	33 9 ± 4 0	83

Table IV Frequency index on admission in patients with heart rates of 100 per minute or more

Group	Number	Frequency index	Mean heart rate
Control	31	13 5 ± 1 5	116
Rheumatic fever			
Normal heart	12	6 6 ± 1 4	115
Carditis	41	6 8 ± 1 6	127

Table V Frequency index on admission and on discharge in patients with rheumatic fever

Group	Number	On admission		On discharge	
		Index	*Mean heart rate*	*Index*	*Mean heart rate*
Normal heart	27	18 9 ± 3 0	96	10 4 ± 2 2	91
Carditis	58	14 6 ± 2 0	116	10 6 ± 2 0	99

Table VI Recurrence group age and sex

Number	Age (years)		Boys	Girls
	6–10	11–17		
50	15	35	23	27

Table VII Frequency index in recurrence group on admission and in carditis group on admission and on discharge

Group	Number	Frequency index	Heart rate
Recurrence	50	6 3 ± 1 2	98
Carditis on admission	58	14 6 ± 2 1	116
Carditis on discharge	58	10 6 ± 2 0	99

Table VIII Frequency index in recurrence and carditis groups at heart rates of under 100 per minute and 100 per minute and over

Group	Number	Under 100 per minute	Mean heart rate	Number	100 per minute and over	Mean heart rate
Recurrence	26	9 2 ± 2 0	84	24	3 3 ± 0 6	114
Carditis	1	33 9 ± 4 0	83	41	6 8 ± 1 6	127

Table IX. Frequency index on admission patients 6 10 years old

Group	Number	Frequency index	Heart rate
Control	49	25 3	89
Rheumatic fever			
Normal hearts	15	27 1	91
Carditis	36	14	115
Landtman[11] (1947)			
Control	50	13 5	89
Carditis	50	6 1	97

ditis group the rate was 116 per minute In order therefore to eliminate the variation of heart rates only patients with rates of less than 100 per minute were included in Table III These results suggested that the lower frequency index in patients with carditis was due to the higher average heart rates in this group However when the index at fast rates was investigated (Table IV) a significant decrease was found in the normal heart and carditis groups as compared with the control group It is possible therefore that the two heart rate groups did not behave uniformly and that there was a slow rate group which did not differ from controls and a fast rate group in which sinus arrhythmia was less than that in controls Unfortunately the carditis group (Table IV) had a faster average heart rate (127) than did the control or normal heart groups so that it is not certain how big a part tachycardia was playing but it is interesting that at fast rates the normal heart group behaved in the same way as the carditis group having a lower frequency index than controls at almost identical heart rates

The changes in the frequency index by the time of discharge were also interesting The most significant change was in the normal heart group which showed a marked drop in the frequency index This resulted in both the normal heart and carditis groups having very similar indices at the time of discharge

Our results on admission were similar to those of Landtman [11] who showed that patients with rheumatic heart disease had less sinus arrhythmia than did a group of controls Since age influences sinus arrhythmia we have included in Table IX only those patients who were between 6 and 10 years of age so that Landtman's figures can be compared with ours It can be seen that the differences between the control and carditis groups were similar to those of Landtman's but the figures themselves show a marked difference In general the values both for our control and carditis groups were about twice those of Landtman's It is possible that some of this difference in the carditis group was due to the fact that in our analysis we separated those patients who were suffering an initial attack of rheumatic fever from those who had had more than one attack but this does not account for the difference between the control groups wherein the average heart rates were identical 89 per minute However Schlomka[23] and Nordenfelt[24] found a frequency index of about 17 in a group of children who ranged in age from 6 to 15 years and this figure is similar to the 23 for our controls who were 6 to 17 years of age Thus there has been considerable variation in the frequency indices in control groups previously reported on

When we investigated the recurrence group we found that sinus arrhythmia was less marked than in those patients who were suffering an initial attack However by the time of discharge the frequency index of the latter group was very similar to that of the recurrence group at the time of admission We are unable to explain this decrease at the time of discharge nor the low frequency index in the recurrence group on admission but these changes would be in keeping with a theory suggested by Weber[25] that the sinus node contains a Kontraktionssubstanz necessary for its normal function and that this substance might be injured by the rheumatic process [11]

We would like to postulate tentatively that the node is damaged by the initial

rheumatic attack and that the injury persists as shown by the decreased sinus arrhythmia at the time of discharge and a similar low frequency index in patients with recurrences at the time of their admission

Summary

1 The degree (frequency index) of sinus arrhythmia was investigated in children suffering an initial attack of rheumatic fever (with and without carditis) in children with a recurrent attack and in children with normal hearts who served as controls

2 At slow heart rates (less than 100 per minute) there was no difference between the control normal heart and carditis groups at the time of admission but a highly significant decrease was observed in the recurrence group

3 At fast heart rates (100 per minute and more) both the normal heart and carditis groups on admission showed a significant decrease in sinus arrhythmia as compared with the control group and the recurrence group showed a significant decrease as compared with the normal heart and carditis groups

4 At the time of discharge the normal heart and carditis groups showed similar values the values for the former had decreased more than had those for the latter as compared with the admission values

5 It is suggested that the fall in sinus arrhythmia observed between admission and discharge and the low frequency index of sinus arrhythmia in the recurrence group may be due to permanent damage to the sinus node by the rheumatic process

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REFERENCES

1 Ludwig C F De l influence de la respiration sur la circulation Quoted by Fredericq
2 Einbrodt P De l influence de la respiration sur la circulation Quoted by Fredericq
3 Brodie T G and Russell A E On reflex cardiac inhibition J Physiol 26 92 1900
4 Hooker D R May reflex cardiac acceleration occur independently of the cardio-inhibitory center? Am J Physiol 19 417 1907
5 Sanderson J B Influence exerted by the movements of respiration on the circulation of the blood Brit M J 1 411 1867
6 Hering E De l influence de la respiration sur la circulation Quoted by Fredericq
7 Fredericq L De l influence de la respiration sur la circulation Arch Biol 3 55 1882
8 Spehta F Sur les modifications respiratoires du rythme cardiaque Arch ital biol 35 277 1901
9 Bainbridge F A The influence of venous filling upon the rate of the heart J Physiol 50 65 1915
10 Sassa K and Miyazaki H The influence of venous pressure upon the heart rate J Physiol 54 203 1920
11 Landtman B Heart arrhythmias in children Acta paediat (Suppl 1) 34 16 1947
12 Mackenzie J *The study of the pulse* Edinburgh and London 1902 Pentland p 86
13 Mackenzie J *Principles of diagnosis and treatment in heart affections* London 1916 Hodder & Stoughton p 138
14 Parkinson J and Gowe A H The heart and its rhythm in acute rheumatism Quart J Med 23 363 1930
15 McCrudden F H Sinus respiratory arrhythmia in children with rheumatic heart disease J A M A 86 535 1926
16 Lounds A A *The heart beat* London 1953 Lewis p 311
17 Lewis T *Electrocardiography and clinical disorders of the heart beat* London 1949 Shaw p 75
18 Wood P *Diseases of the heart and circulation* ed 2 London 1956 Eyre and Spottiswoode p 213
19 Myers G B *The interpretation of the unipolar electrocardiogram* St Louis 1956 The C V Mosby Company p 89
20 Nordenfelt O Studien uber respiratorische Arrhythmie besonders des Kindesalters Arch Kreislaufforsch 13 97 1943
21 United States–United Kingdom Cooperative Council Trial of ACTH Cortisone and Aspirin The treatment of acute rheumatic fever in children Circulation 11 343 1955
22 Massell B F Jhaveri S and Czoniczer G Therapy and other factors influencing the course of rheumatic heart disease Circulation 20 737 1959
23 Young E Liebman J and Nadas A S The normal electrocardiogram of children Am J Cardiol 437 1960
24 Schlomka G and Reindell H Untersuchungen uber die physiologische Unregelmassigkeit des Herzschlages Ztschr Kreislaufforsch 28 473 1936
25 Schlomka G Untersuchungen uber die physiologische Unregelmassigkeit des Herzschlages Ztschr Kreislaufforsch 29 510 1937
26 Weber A Betrachtungen uber die rhythmische Herzkontraktion Ztschr Kreislaufforsch 31 186 1939

Essential hypertension with an elevated noradrenaline excretion

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Shortly after noradrenaline was discovered as the neurohormone of the sympathetic nerves a number of papers appeared postulating a possible correlation between essential hypertension and an increase in the output of noradrenaline In general these papers did not demonstrate any significant relationship between the output of noradrenaline and the hypertension However von Euler and associates[4] did show that 16 4 per cent of their hypertensive patients had an abnormally high output of noradrenaline and Holtz and associates believed that the urine from hypertensive patients showed a somewhat higher content of noradrenaline than did that from normal subjects

When one considers all of the many possible causes of essential hypertension and the relationship of the sympathetic nerves to the control of human blood vessels it certainly seems reasonable to assume that at least in some hypertensive patients the etiology is directly related to an increase in the activity of the sympathetic nerves The purpose of this paper is to demonstrate the possibility of such a relationship

Methods

Determinations of urinary catechol amines were made on approximately 500 patients with an elevated systolic and diastolic blood pressure the range of elevation of the blood pressure and the intensity of the illness varied greatly Of the 500 patients 2 subjects with an elevated blood pressure and an increase in the urinary output of noradrenaline were selected for a more thorough evaluation

1 General The 24 hour urines were collected acidified and assayed for adrenaline and noradrenaline Collections were made at the time of admission at various other times during hospitalization and after discharge

2 Preparation of urine extract The urine was hydrolyzed and the adrenaline and noradrenaline selectively adsorbed on aluminum hydroxide and filtered The precipitate was washed and redissolved with 2N sulphuric acid The remaining salts were precipitated out by mixing the extract with alcohol and acetone The filtrate was concentrated in vacuo The method of extract preparation and bioassay has been described in detail elsewhere [7,8]

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3 Biologic assay The blood pressure of the cat was used in conjunction with the rectal cecum of the hen

A BLOOD PRESSURE OF CAT The blood pressure of the cat was recorded from the carotid artery and injections of adrenaline noradrenaline and urinary extract were made into the femoral vein

B RECTAL CECUM OF HEN Two to three centimeters of the rectal cecum of the hen was suspended in Tyrode s solution at 39°C Injections of adrenaline, noradrenaline and urinary extract were made into the bath and the degree of cecal relaxation was recorded

C COMPUTATION OF RESULTS After determination of the activity ratio for adrenaline and noradrenaline on the blood pressure of the cat and the rectal cecum of the hen and the activity of the unknown urinary extract in terms of l noradrenaline it is possible to calculate the relative amounts of adrenaline and noradrenaline in the urinary extract

4 Fluorometric assay The fluorometric method of von Euler and Floding[10] was used to screen all patients This method depends upon the differential oxidation rate of adrenaline and noradrenaline at pH 6 0 and pH 3 5 At pH 6 0 both catecholamines are oxidized within a period of 2 minutes whereas at pH 3 5 the adrenaline in the presence of zinc sulfate is completely oxidized within 3 minutes but only 5 per cent of the noradrenaline is oxidized Urine from those patients who showed fluorometrically an elevated output of adrenaline and/or noradrenaline was also bioassayed for adrenaline and noradrenaline A Farrand Model A fluorometer was used to measure fluorescence

Results

The normal 24 hour output varies from 10 to 30 μg for adrenaline and from 20 to 60 μg for noradrenaline Calculated on the basis of a 24 hour output the average quantity of adrenaline and noradrenaline excreted by normotensive adult males was 15 7 and 32 3 μg respectively These normal results compared well with those of von Euler

Of the 500 hypertensive patients followed 73 9 per cent showed a normal output of noradrenaline However 10 8 per cent were shown to have a urinary output of noradrenaline in excess of 90 μg per 24 hours 5 5 per cent in excess of 120 μg per 24 hours and 3 0 per cent in excess of 180 μg per 24 hours (see Table I) Of the patients who had an output of noradrenaline in excess of 180 μg per 24 hours 76 6 per cent were proved surgically to have a pheochromocytoma since the urinary noradrenaline was persistently greatly elevated (300 to 3 190 μg per 24 hours) in the patients with pheochromocytoma there was no difficulty in delineating this group of patients from the other hypertensive subjects with an elevated output of noradrenaline

The two specifically selected cases are summarized in the following paragraphs

Case 1

Clinical summary E E 40 year-old white highway patrol dispatcher entered the hospital on March 27 1956 with the chief complaint of blurring of vision He had considered himself to be in good health until 15 years previously (age 25) when he was found to have elevated blood pressure (exact level not known) In the following year he developed early morning occipital headaches which became increasingly more severe On follow up examinations he was found to have blood pressure level of 150/100 to 180/110 mm Hg Two years prior to admission he noted dyspnea on exertion easy fatigability syncopal attacks related to exercise and increased emotional irritability Four days prior to admission he noted blurring of vision

Family history The patient s father died at age 50 of a stroke following long standing arterial hypertension the paternal aunt had also died of hypertension

The patient was the oldest of 3 children of a couple in the lower middle-income group He related that his father had been a firm restrictive individual and that he had not felt close to him He was always his mother s favorite He emphasized that he never felt quite sure of himself and always depended upon his mother for help and direction. He characterized himself as an individual who did not express his feelings easily particularly those of hostility

He married at the age of 23 years but maintained close ties with his mother his mother lived nearby and each day he visited her He reported that his wife and mother were antagonistic to each other and although he often felt his wife s position to be correct he could not bring himself to the point of contradicting or openly differing with his mother He recognized that the increasing feelings of nervousness and irritability were directly related to these relationships involving his wife and mother and this in turn led to feelings of doubt and anger— I feel all bottled up tight blue.

On physical examination the blood pressure

Table I. Distribution of noradrenaline excretion in 500 cases of idiopathic hypertension (all figures are in μg per 24 hours)

	Urinary noradrenaline (in μg per 24 hours)						
	<30.0	30.0 to 60.0	60.0 to 90.0	90.0 to 120.0	120.0 to 140.0	140.0 to 180.0	180.0
Per cent distribution	36.5	37.4	15.0	5.3	1.0	1.5	3.0
	Total normal output is 73.9%		Fringe group 15.0%	Total hypersecretion is 10.8%			

with the patient lying and sitting was 260/170 mm. Hg; the pulse was 120 per minute. Positive findings included the following: Funduscopic examination revealed bilateral papilledema, extensive hemorrhages and exudates, arteriolar narrowing with areas of focal constriction, and fullness of the veins. The heart was not enlarged. The aortic second sound was loud and snapping. The mitral first sound was accentuated. Neurological examination revealed a decrease in visual acuity, but the findings were otherwise unremarkable.

Accessory clinical findings. Hemoglobin was 14.6 Gm. per cent; white blood cell count, 12,500/mm.; differential, normal. Urinalysis: pH, 5.5; specific gravity, 1.010; traces of protein; 1-2 white cells; no casts on microscopic examination. Fishberg concentration test: specific gravity, 1.016; phenolsulfonphthalein excretion, 65 per cent in 2 hours. The nonprotein nitrogen was 34 mg. per cent; cholesterol, 320 mg. per cent; fasting blood sugar, 129 mg. per cent; protein-bound iodine, 9.8 mg. per cent; basal metabolic rate, −9 per cent; I[131] uptake, 35 per cent; sodium, 143 mEq./L.; potassium, 3.5 mEq./L.; CO_2, 33 mEq./L.; chloride, 100 mEq./L.; glucose tolerance test: fasting, 111; 1 hr., 87; 2 hr., 704; 3 hr., 80 mg. per cent. Electrocardiogram: left ventricular ischemic pattern. X-ray films: skull and chest, normal. Intravenous pyelogram: right bifed renal pelvis and ureter without stones or distortion.

Regitine test and Amytal test both resulted in modest falls in blood pressure, but neither exceeded 40 mm. Hg systolic pressure or 20 mm. Hg diastolic pressure. These drops were transient in both instances.

The patient was begun on a dietary regimen of rice and fruit and treated with Ansolysen, reserpine, and Apresoline. Furthermore, efforts were directed toward readjusting his domestic life. Gradually, during the next 6 weeks, the blood pressure fell to 160/100 and 150/80 mm. Hg. The papilledema receded by the fifth week, and almost all hemorrhages and exudates had resolved by the twelfth week. His activity was gradually increased, and after 3½ months of hospitalization he was discharged.

He returned to work but noted the development of weakness and easy fatigability. Readings of blood pressure taken at home gradually increased in spite of conscientious use of medication and restriction of the intake of salt. He was then readmitted to the hospital on Nov. 19, 1956, for re-evaluation.

Physical examination at this time demonstrated a blood pressure of 160/110 and 230/130 mm. Hg with the patient standing and lying, respectively. The pulse rate was 104. There was some increase in the light reflex to the arterioles of the fundi, and the aortic second sound was accentuated.

Accessory clinical findings. Maximum concentration of urine was 1.018; phenolsulfonphthalein, 65 per cent in 2 hours; I[131] uptake, 21 per cent in 24 hours; oral glucose tolerance, decreased. Regitine test was negative. 24-hour excretion of 17-ketosteroids was 20.0 mg.

The course in the hospital was primarily concerned with the regulation of his drug therapy and counseling for the depressive reaction. After 2 months his blood pressure was maintained at 120/80 mm. Hg. He was discharged and has returned to work, continuing his program of restricted intake of salt and antihypertensive medication.

Catecholamine summary. On admission, two 24-hour samples of urine were collected and bioassayed for adrenaline and noradrenaline. This was repeated during hospitalization, at the time of discharge, and 1 year later. The results of these findings show that the sympathetic nervous activity as represented by the urinary noradrenaline was markedly elevated on admission (182.0 μg per 24 hours), but during the course of treatment this gradually decreased so that by the time of discharge it was almost within normal limits. Two years subsequent to discharge the noradrenaline had declined to 15.8 μg per 24 hours, or that is, it was within normal limits. There was a commensurate decline in the blood pressure (see Table II). The urinary adrenaline, on the other hand, varied from specimen to specimen and in general was slightly elevated.

Case 2

Clinical summary. N. S., a 31-year-old white married woman, was first found to have an elevated blood pressure 2 years prior to admission during the last trimester of her second pregnancy. She had always considered herself to be in excellent health until that time. She was placed on reserpine and, although increasingly larger doses were required

the blood pressure was controlled at normotensive levels The delivery was uncomplicated During the postpartum period the blood pressure remained elevated whenever withdrawal of medication was attempted Frontal headaches developed and were occasionally relieved by aspirin The headaches were nonpulsatile in type and at times were apparently related to specific life situational stresses

In the 6 months prior to the initial hospitalization he had discontinued all medication but noted increasing feelings of depression and had begun to use alcoholic beverages frequently

There was a family history of hypertensive vascular disease The father died at age 44 of cardiac failure secondary to hypertension a younger sister died 1 year previously of a subarachnoid hemorrhage having had recognized hypertension for 5 years

The recent personal history was marked by periods of intense conflict and unrest The patient was the oldest of 2 children born to a couple in the upper income group She considered her family a tightly knit comfortable group She felt closest to her father and experienced a period of deep depression at the time of his death Shortly after her father death her sister died and the patient became quite morose Her excessive intake of alcohol began at this time.

In the month preceding the first admission she had experienced increasing conflict with her husband concerning his relationship to her and the two children.

On physical examination the blood pressure was 160/90 mm Hg the pulse was 72 She appeared fatigued and anxious Funduscopic examination clear The lungs were clear The heart was normal in size. The aortic second sound was accentuated There were no murmurs

Accessory clinical findings Hemoglobin was 11 6 Gm per cent white blood cell count ? 200/mm normal differential Urinalysis specific gravity 1 012 traces of protein clear on microscopic examination Regitine test was normal Phenolsulfonphthalein excretion total was 70 per cent in 2 hours Nonprotein nitrogen was 24 mg per cent fasting blood sugar 110 mg per cent cholesterol 175 mg per cent Electrocardiogram was normal Chest x ray examination was normal Intravenous pyelogram was normal

While in the hospital the patient was placed on modified bed rest Gradually the level of the blood pressure decreased and after 1 week was 130/70 mm Hg During hospitalization he was frequently seen by her attending psychiatrist

During the ensuing 20 months the level of the blood pressure fluctuated markedly During this period she received intensive psychotherapy and there was some modification of her adjustment problems She received mild sedative therapy in addition No specific antihypertensive medications were employed

Catecholamine summary On admission the 24 hour urinary noradrenaline was 98 4 μg and 3 weeks later it was 182 5 μg The blood pressure on admission was 150/100 mm Hg As the patient responded to treatment the high output of noradrenaline gradually decreased so that at the time of discharge it was 27 0 μg that is well within normal limits There was a corresponding decline in the blood pressure (see Table II) The output of adrenaline remained for the most part within normal limits

Discussion

Sympathetic nerves carry vasoconstrictor fibers to arteries arterioles and arteriovenous anastomoses It is now generally accepted that the neurotransmitter substance of the sympathetic (adrenergic) nerves is noradrenaline [1] and that this hormone is released as such at the sympathetic nerve endings Furthermore under increased activity of the sympathetic nerves such as that resulting from specific emotional[11,14] or physical stresses [15,4] there is an increase in the release of this hormone and this increase in release is reflected in the urine as an elevation in the urinary output of free and conjugated noradren

Table II Output of noradrenaline and adrenaline in 2 hypertensive subjects who showed clinically an increase in sympathetic nerve activity

Subject	Specimen number	Date of collection	Adrenaline (μg/24 hr)	Noradrenaline (μg/24 hr)	Blood pressure (mm Hg)
Case 1 (E E)	1	March 30 1956	25 0	182 0	260 170
	2	May 2 1956	41 0	83 9	140/90
	3 (Discharged)	Oct. 22 1956	65 7	5 0	160/110
	4	Sept. 20 1959	21 7	15 8	140/90
Case (N S)	1	Feb 26 1958	37 6	98 4	150/100
	2	March 11 1958	1 3	182 5	140/90
	3	March 24 1958	11 3	136 0	140/90
	4	June 9 1958	47 5	33 4	140/80
	5	Sept 11 1959	18 1	27 0	130/70

aline It is well established that noradrenaline elevates the blood pressure[17,18]

Although noradrenaline is also found in the adrenal medulla the principal hormone of the human adrenal medulla is adrenaline [9] Both of these hormones are released in increased amounts under various forms of stress i e burns [8] muscular exercise [15] centrifugation [16] X irradiation [22] etc

Since adrenaline is a general vasodilator [7,19] hypertension could not result from any increase in the output of adrenaline On the other hand noradrenaline elevates both the systolic and diastolic blood pressure [7,9] and therefore an increase in the activity of the sympathetic nerves with a concomitant increase in the release of noradrenaline could produce a hypertensive state However it should also be emphasized that a large number of hypertensive subjects with increased vasomotor activity do not show an elevation in the output of noradrenaline therefore their hypertension must be the result of something other than an increase in sympathetic nerve activity (see Table I normal output)

Although this paper describes in detail only 2 cases of idiopathic or essential hypertension it demonstrates that at least in these 2 cases the hypertension seems to result from an increased sympathetic nerve activity as manifested by an increase in the urinary output of the sympathetic neurohormone noradrenaline Furthermore it would appear that this increase in sympathetic nerve activity in turn was related in these particular patients to an increase in activity of such higher nerve centers as the cortex since both of these patients were greatly disturbed over their personal and domestic problems Therefore one would seem justified in concluding that possibly other such similar hypertensive cases exist and that these should be searched for and studied in detail

REFERENCES

1 Euler U S v A specific sympathomimetic ergone in adrenergic nerve fibers (Sympathin) and its relation to adrenaline and noradrenaline Acta physiol scandinav 12 73 1946

2 Holtz P Credner K and Kroneberg G Über das sympathicomimetische pressorische Prinzip des Harns (Urosympathin) Arch exper Path Pharmakol 204 228 1947

3 Goldenberg M and Rapport M M Norepinephrine and epinephrine in human urine (Addison disease essential hypertension pheochromocytoma) J Clin Invest 30 641 1951

4 Euler U S v Hellner S and Purkhold A Excretion of noradrenaline in urine in hypertension Scandinav J Clin & Lab Invest 6 54 1954

5 Barcroft H and Swan H J C Sympathetic control of human blood vessels London 1953 Edward Arnold & Co

6 Folkow B Nervous control of the blood vessels Physiol Rev 35 629 1955

7 Euler U S and Hellner S Excretion of noradrenaline adrenaline and hydroxytyramine in urine Acta physiol scandinav 22 161 1951

8 Goodall McC Stone C and Haynes B W J Urinary output of adrenaline and noradrenaline in severe thermal burns Ann Surg 145 479 1957

9 Euler U S v and Orwén I Preparation of extracts of urine and organs for estimation of free and conjugated noradrenaline and adrenaline Acta physiol scandinav (Suppl 118) 33 1 1955

10 Euler U S and Floding I Diagnosis of phaeochromocytoma by fluorimetric estimation of adrenaline and noradrenaline in urine Scandinav J Clin & Lab Invest 8 288 1956

11 Goodall McC and Kirshner N Biosynthesis of epinephrine and norepinephrine by sympathetic nerves and ganglia Circulation 1 366 1958

12 Zuidema G D Silverman A J Cohen S I and Goodall McC Catecholamine and psychologic correlates of vascular responses New England J Med 256 976 1957

13 Bergsman A The urinary excretion of adrenaline and noradrenaline in some mental diseases Acta psychiat et neurol scandinav (Suppl 133) 34 1959

14 Euler U S v Gemzell C A Levi L and Ström G Cortical and medullary adrenal activity in emotional stress Acta endocrinol 30 567 1959

15 Euler U S v and Hellner S Excretion of noradrenaline and adrenaline in muscular work Acta physiol scandinav 26 183 1952

16 Goodall McC and Berman M L Urinary output of adrenaline noradrenaline and 3-methoxy-4 hydroxymandelic acid following centrifugation and anticipation of centrifugation J Clin Invest 39 1533 1960

17 Goldenberg M Pines K L Baldwin E Def Greene D G and Roh C E The hemodynamic response of man to norepinephrine and epinephrine and its relation to the problem of hypertension Am J Med 5 792 1948

18 Swan H J C Effect of noradrenaline on human circulation Lancet 2 508 1949

19 Euler U S v Some aspects of the role of noradrenaline and adrenaline in circulation Am Heart J 56 469 1958

20 Euler U S Franksson C and Hellstrom J Adrenaline and noradrenaline content of surgically removed human suprarenal glands Acta physiol scandinav 31 6 1954

21 Goodall McC and Meehan J P Correlation of adrenaline and noradrenaline excretion to g tolerance and g aration Am J Phy iol 187 601 1956

22 Goodall McC and Long M Effect of whole body X irradiation on the adrenal medulla and the hormones adrenaline nd noradrenaline Am J Physiol 197 1265 1959

Effect of variations in cardiac output and diastolic filling period upon the mitral diastolic gradient

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The magnitude of the mitral diastolic gradient in subjects with mitral stenosis is a function of the size of the mitral valve and the subvalvular area, the cardiac output, and the heart rate, especially the diastolic filling period. In patients with atrial fibrillation the diastolic gradient varies from beat to beat with variations in the diastolic filling period.[1,2] A progressive fall in the magnitude of the gradient is observed during the latter portion of a long diastolic interval. Conversely, the mean magnitude of the diastolic gradient is elevated during a short diastolic filling interval.

Since both the heart rate and cardiac output may be increased during exercise, it is often difficult to differentiate between the effects of these two parameters upon the mitral diastolic gradient under exercise conditions. In patients with sinus rhythm the variations in the diastolic interval are limited at rest and during exercise. In contrast, in patients with atrial fibrillation marked variations in the diastolic filling period are usually readily observed both at rest and during exercise. The purpose of this report is to illustrate and differentiate between the effects of variations in diastolic filling period and in flow upon the mitral gradient in 8 subjects with mitral stenosis and atrial fibrillation who were studied by combined right and left heart catheterization. Significant mitral insufficiency was not observed in any of these patients at mitral commissurotomy. Comparable observations have not been previously reported.

Methods and materials

The techniques formerly employed in combined right and left heart catheterization in this laboratory have been described.[1-*] Cardiac output was determined by the Fick principle both at rest and during steady state exercise. The magnitude of the mean diastolic left atrial–left ventricular gradient was determined by planimetry at a paper speed of 75 mm per second. The diastolic interval was

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*Transseptal left atrial puncture and transventricular left ventricular puncture are now utilized for left heart catheterization.

measured as the duration of the gradient The latter was measured as the interval during which left ventricular pressure was equal to or less than left atrial pressure Since the left atrial and ventricular pressure curves were recorded from the same base line and with equisensitive pressure gauges the determination of the exact crossover points of the atrial and ventricular curves was readily accomplished The error in measurement of the diastolic period is estimated to be 0 02 or 0 03 second at most A beat by beat analysis was made of all gradients both at rest and during exercise and the gradients were plotted against the diastolic intervals

Results

The relationships between the mitral diastolic gradient and the diastolic interval of that gradient are illustrated in Figs 1 3 for the 8 subjects studied The X points refer to the exercise data and the black dots to the data obtained at rest The decrement in the magnitude of the

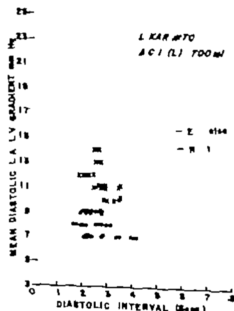


Fig 1 Relationship between the mitral diastolic gradient and the diastolic filling interval at rest and during exercise in Subject L Kar The increment in cardiac index during exercise is also listed The exercise gradients are significantly different from the resting gradients at the same diastolic intervals Oxygen consumption per minute per square meter of body surface area increased from 119 ml at rest to 196 ml during exercise

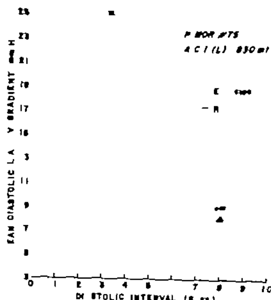


Fig 2 Data for P Mor Oxygen consumption during exercise rose from 111 to 220 ml /min /M

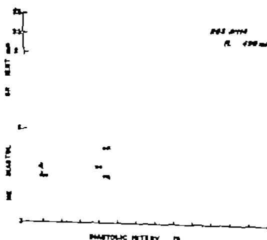


Fig 3 Data for E Ros Oxygen consumption during exercise increased from 104 to 213 ml / min /M

gradient with increasing diastolic intervals is readily noted as is the separation between the exercise and rest data In 7 subjects the exercise gradient is significantly greater than the rest gradient at the same diastolic interval ($p < 0.001$) In one subject (E Coo) no significant difference ($0.2 > p > 0.1$) was noted between the data obtained at rest and those during exercise The clinical and catheterization data for these 8 subjects have been published previously[8]

The exercise output increment

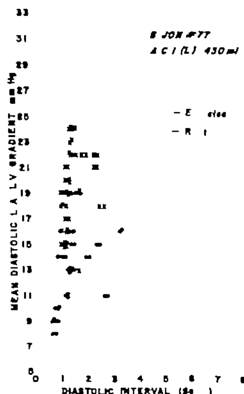


Fig 4 Data for S Jon Oxygen consumption rose from 138 to 227 ml/min/M



Fig 5 Data for S Tal Oxygen consumption increased from 102 to 174 ml/min/M

square meter of body surface area are shown on the graphs *L* refers to output data obtained during combined right and left heart catheterization and *R* to the data determined in the course of the right heart catheterization which was performed immediately prior to the left heart catheterization The clear separation between the resting and exercise gradients in the first 7 subjects is not proportional to the level of increment in cardiac output during exercise Oxygen consumption during rest was approximately doubled during exercise in these 8 patients

Discussion

Hemodynamic measurements during exercise are frequently performed during right heart catheterization in subjects with mitral valvular disease Increments in pulmonary arterial pressure under such circumstances may be due to alterations in such parameters as cardiac output heart rate pulmonary blood volume left atrial mean pressure left ventricular end diastolic pressure intrathoracic and pleural pressure and pulmonary arterial vasomotion Determination of the mean diastolic left atrial–left ventricular gradient during rest and exercise studies affords a more direct method of evaluating the status of the mitral valve Increments in cardiac output and heart rate may both increase the magnitude of the mitral gradient If the increase in heart rate is the primary factor in the increase in gradient during exercise intravenous atropine might theoretically be employed to simulate exercise hemodynamics If the effects of increments in flow

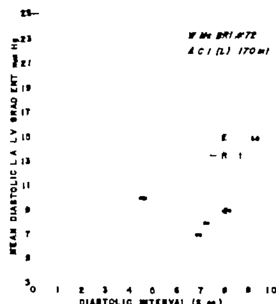


Fig 6 Data for W McBri Despite the minimal rise in cardiac output during exercise there is a significant difference between the gradients at rest and during exercise Oxygen consumption increased from 115 to 224 ml/min/M

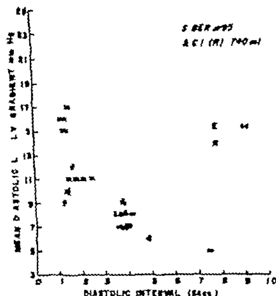


Fig 7 Data for S Ber Exercise output data were obtained during right heart catheterization Oxygen consumption rose from 100 to 222 ml/min /M

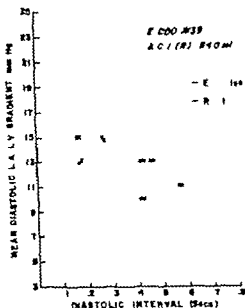


Fig 8 Data for E Coo There is no significant difference between the gradients obtained at rest and during exercise The increment in oxygen consumption is from 115 to 2 5 ml /min /M

can be separated from those of rate per se intravenous administration of atropine (unless accompanied by an increase in cardiac output) could not be utilized to simulate exercise conditions The data obtained in the 8 patients in this study demonstrate that in most patients even small increments in flow result in separation of the resting and exercise gradients at the same diastolic time intervals

The magnitude of the mitral valvular gradient in any one patient with mitral stenosis is a function of the size of the valve amount of flow through the mitral valve (or cardiac output in the absence of mitral insufficiency) and the diastolic filling period Since the latter period shortens proportionately more than total cycle length as the heart rate is increased the magnitude of the gradient rises during tachycardia per se The separation between the exercise and rest gradients noted in this study at the same diastolic filling intervals demonstrates that the flow increment during exercise also contributes to the gradient increment observed during exercise

Summary

The differential effects of alterations in the diastolic filling period of the left ventricle and in cardiac flow upon the mean diastolic left atrial–left ventricular gradient have been investigated in 8 subjects with atrial fibrillation studied at diastolic filling intervals of similar magnitude The results demonstrate the sensitivity of the magnitude of the gradient to even small alterations in blood flow

REFERENCES

1 Litwak R S Samet P Bernstein W H Silverman L H Turkewitz H and Lesser M E The effect of exercise upon the mean diastolic left atrial-left ventricular gradient in mitral stenosis J Thoracic Surg 34 449 1957

2 Samet P Litwak R S Bernstein W H Fierer E M and Silverman L M Clinical and physiologic relationships in mitral valve disease Circulation 19 517 1959

3 Braunwald E Moscovitz H L Amram S S Lasser R P Sapin S O Himmelstein A Ravitch M M and Gordon A J The hemodynamics of the left side of the heart as studied by simultaneous left atrial left ventricular and aortic pressures particular reference to mitral stenosis Circulation 12 69 1955

Experimental and laboratory reports

Analysis of time and concentration components and cardiac output determination obtained from precordial isotope-dilution curves

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Analysis of precordial isotope dilution curves has proved to be a useful technique for serial determinations of cardiac output. Although previous studies[1-14] have outlined the basic technique, necessary calculations, and the close agreement with determinations of output by conventional methods, little information has been accumulated other than that presented by Shackman[16] on the repeatability of these measurements such as that available for the Fick method.[17] Perhaps because of the variability in instrumentation, few systematic analyses of the time components of the resultant curves, such as those presented by Cornell and associates,[15] have been made. Such an approach has increased the screening value of arterial dye dilution curves in various disease states and might be applicable to precordial curves when obtained by a standard technique.

Doses of radioactive iodinated human serum albumin (RIHSA) necessary to obtain satisfactory results have been substantially reduced over those usually reported, probably because of increasing sensitivity of detection equipment. Thus analysis of curve contours could be widely applied in screening clinics as well as diagnostic laboratories if it were possible to establish the range of variability present in groups of normal subjects.

The purpose of this report is to present further data comparing precordial isotope dilution cardiac output values with those obtained by the Fick method, to report on the repeatability of this measurement, and to attempt to quantify the contour characteristics of normal curves.

Materials and methods

Ninety precordial isotope dilution curves (determinations of cardiac output) in 42 patients with no evidence of cardiac disease (34 males and 8 females) have been analyzed. Thirty-four studies were obtained in 15 patients who had cardiac outputs determined according to the Fick principle by means of right heart catheterization. The latter studies were consecutive rather than simultaneous. All patients were in the supine position during the procedure.

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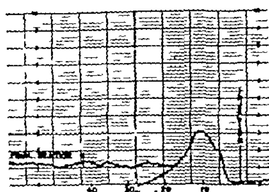


Fig. 1 Probe focused over apex of heart, fifth left intercostal space in the mid-clavicular line. Cardiac index 4.33 L/min/M

The method of right heart catheterization in this laboratory has been described elsewhere

Externally monitored isotope dilution curves were obtained by positioning a collimated scintillation detector in direct contact with the skin over the second left intercostal pace or apex. The detector employed in the probe was a 2.5 by 2.5 cm thallium activated sodium iodide crystal shielded with a 2.5 cm thick straight bore lead collimator with a diameter of 2.5 cm and a depth of 3.8 cm beyond the crystal

The scintillation probe was connected to a Nuclear Chicago rate meter with a variable time constant which was set at 2.0 seconds. Dose was dependent on the selection of count rate which ranged between 3,000 and 30,000 counts per minute. Curves were recorded on a direct writing linear recorder with a paper speed of 6 inches per minute

The RIHSA was delivered through a three way stopcock attached to an indwelling No 20 Riley needle placed in an antecubital vein. Rapid injection of the RIHSA contained in a volume of 1 ml was followed by a 10 ml flush of normal saline solution. Injection time was marked on the base line and recording was continued through the primary phase and recirculation. Ten minutes after injection with the apparatus remaining in place a final concentration (Ceq) was recorded over a 1 minute period. Radioactivity per study ranged from 5 to 45 microcuries (μc)

In some subjects the blood volume was determined by the RIHSA method; a single channel gamma ray spectrometer and scintillation well counter were employed for the counting of blood samples and standard which were 3 ml in volume. In the others the blood volumes were estimated from normal standard

The curves were extrapolated to the base line by *plotting points from the* descending limb on semilogarithmic paper and then replotting the extrapolation on the initial linear tracing (Figs 1 and 2). The area under the curve was determined by a compensating planimeter and cardiac output was calculated according to the formula

$$F = \frac{Ceq \times BV}{Cavg \times T}$$

F represents flow. Ceq is the final concentration. Cavg is the average concentration during time T and T is the time of primary passage of indicator through the heart

The time components of the curves were

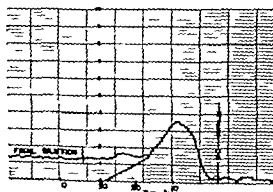


Fig. 2 Probe focused over second left intercostal space adjacent to sternum. Cardiac index 4.45 L/min/M

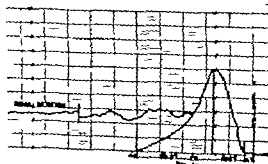


Fig. 3 Probe focused over second left intercostal space adjacent to the sternum. Appearance time (*AT*), build up time (*BT*), disappearance time (*DT*). Cardiac index 3.40 L/min/M

Table I

Ratio	Normal (41 curves) Mean	Normal (41 curves) S.D.	Shunts (38 curves) Mean	Shunts (38 curves) S.D.	p value
$\frac{Cp + BT}{Cp}$	0.54	±0.18	0.71	±0.13	< .001
$\frac{Cp + 2BT}{Cp}$	0.32	±0.18	0.57	±0.19	< .001

analyzed according to methods widely applied to arterial dye dilution curves.[2-4] Appearance time (A.T.) is the number of seconds from the instant of injection to the onset of the upstroke. Build-up time (B.T.) is the number of seconds from the onset of upstroke to the peak of the curve. Disappearance time (D.T.) is the time from the peak to the return of the extrapolated disappearance slope to the base line (Fig. 3). The D.T. divided by the B.T. constitutes the D.T./B.T. ratio and should correct for generalized slowing of time components as occurs with reduced cardiac output or increased volume.[3] A number of curves were analyzed for the disappearance ratios

$\frac{Cp + BT}{Cp}$ and $\frac{Cp + 2BT}{Cp}$ described by

Carter and associates.[22] In addition the ratio obtained by dividing the height at the peak in centimeters (Cp) by the height of the recirculation level (C_R) in centimeters (Cp/C_R ratio) was employed. When an identifiable recirculation peak was not present the C_R height was taken 25 seconds after injection (the mean time for C_R of the normal subjects).

The standard deviation, correlation coefficient, standard error of a single observation, and standard t test were applied according to the methods of Hill[7] and Mainland.[8]

Results

Analysis of curve contours. Ninety studies from 42 normal subjects resulted in appearance times of 11.5 seconds, rapid upstroke, and an exponential fall-off followed by recirculation and a final concentration level. Generally, curves recorded over the apex were somewhat more spread out than those from the second left intercostal space, having longer build-up (B.T.) and disappearance (D.T.) times but essentially similar D.T./B.T. ratios.

Mean B.T. was 9.9 ± 2.9 sec., D.T. was 34 ± 9.2 sec., and the D.T./B.T. ratio was 3.9 ± 1.9. Comparable studies on 32 curves from 18 patients with proved left-to-right shunts yielded the following values: B.T. of 8.3 ± 4.4 sec., D.T. of 61.5 ± 25.4 sec., D.T./B.T. ratio of 8.2 ± 2.9. Only 3 of 32 curves in this group resulted in D.T./B.T. ratios of less than 5.0, and each of the 3 patients had one or more repeat studies in which the D.T./B.T. ratio was more than 5.0. Whereas the differences in B.T. values were insignificant, the values obtained for the D.T. and D.T./B.T. ratios between the two groups were significantly different (p < .001).

Comparison of 38 curves from 18 patients who had proved shunts with those from 57 normal subjects utilizing the Cp/C_R



Fig. 4. Comparison of normal and abnormal curves by the Cp/C_R ratio. Each dot represents Cp/C_R ratio of curves obtained in normal subjects and each circle the Cp/C_R ratio of curves obtained in abnormal subjects. Solid line represents mean and dotted line the limit of one standard deviation.

Table II

	Number of successive curves	First group (Mean ± S D)	Second group (Mean ± S D)	p value
D T/B T ratio	40	5 5 ± 3 4	5 5 ± 3 0	>0 9
$\frac{Cp+BT}{Cp}$ ratio	28	71 ± 14	71 ± 13	>0 9
Cp/Ca ratio	46	1 91 ± 50	1 89 ± 10	>0 3

ratio revealed a mean ratio of 2 6 ± 0 55 in the normal and a mean of 1 4 ± 0 59 in the abnormal (Fig 4) Analysis showed these differences to be significant ($p < 001$)

The results of comparisons utilizing other disappearance ratios are given in Table I and the repeatability of the various disappearance ratios are shown in Table II

Comparison of precordial isotope dilution and Fick outputs Comparison of isotope data with data obtained by the Fick method in 15 catheterized patients showed good agreement between the two techniques (r = +0 97) with deviations of the isotope dilution measurement from the Fick values ranging from −16 to +10 per cent Mean deviation was 8 8 per cent (Fig 5 Table III) Mean cardiac index by the isotope method was 3 44 ± 0 31 L /min M

Repeatability of precordial isotope dilution cardiac output determinations Two successive cardiac outputs were determined in 37 normal subjects 3 successive studies in 4 subjects and 4 successive studies in 1 subject (total radioactivity injected into the latter was 93 μc) The mean value for the 42 initial studies was 5 67 L /min ± 1 84 The mean for the 42 second studies in the e same individuals was 5 54 L /min ± 1 43 The differences were not significant ($p > 0 9$) The standard er or of an individual determination of output was 0 31 L min Mean cardiac index for the entire eries was 3 71 ± 0 30 L /min /M

Discussion

The close agreement between the outputs determined by the isotope dilution method and those obtained according to the Fick principle in this study lends further support to the previous data of others who reported nearly identical results from isotope dilution dye dilution and Fick techniques [7 ... 11 15]

The good reproducibility of results from repeated curves obtained in the same individual demonstrate that the slight variations in the recorded curves are of no significance for this determination The results confirm the relative stability of successive determinations of cardiac output in supine subjects as shown by the Fick method The values obtained for cardiac index and standard error of a single determination in the normal subjects who did not have Fick determinations compare favorably with those obtained by the Fick method in normal subjects as reported in the literature [7]

Precordial isotope dilution curves provide a convenient means of screening

Table III. *Comparison of Fick and precordial output*

Subject	Precordial (L /)	Fick (L /min)
1	3 5	3 5
2	4 3	4 5
3	5 9	5 4
4	9 7	11 3
	4 2	4 4
6	6 6	6 0
7	3 2	3 4
8	8 4	8 7
9	4 2	4 0
10	6 2	6 3
11	7 5	8 5
1	6 2	6 7
13	5 0	5 7
14	5 4	6 4
15	4 9	4 5
Mean	5 68	5 93
S D	±1 76	±2 11

= +0 97

*These patients were excluded from this study because they ... during ... of the pulmonary ... tion phase

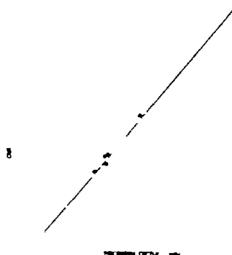


Fig Comparison of Fick and precordial output on 15 subjects (= +0 97)

patient for certain disease states by comparison of the time component relationships with those obtained from a normal control group In addition analysis of successive curves in the same patient for D T B T Cp C_R and disappearance ratios give good reproducibility Reliable serial determinations of cardiac output may be readily made from those patients who have normal curves

The derivation of normal values for selected time components of precordial isotope-dilution curves might allow such analyses of the curves to aid in the detection and evaluation of such pathologic conditions as congestive heart failure left to-right shunting and valvular insufficiency as is the case with conventional dye-dilution techniques In order to obtain relatively reproducible curves in individual subjects it was necessary to follow a rigid routine of rapid injection with immediate flush while focusing as accurately as possible over the selected sites One could thus deliver the indicator as a bolus to the central circulation as well as avoid distortions of the curve that are known to occur when counting is done over the right atrium or great veins[9, 4]

With the technique employed appearance time was a variable and unreliable component Its length was probably as closely related to speed of injection and the distance from antecubital fossa to heart as it was to the subject s circulation time Injection into the femoral vein without flush might provide better values for appearance time In some patients with heart failure the appearance time has been greatly prolonged but in a limited series of patients with right to left shunts it has not been helpful Simultaneous detection over the heart and a peripheral artery has been demonstrated to be useful in the detection of right to left shunting[24]

Values for B T and D T and D T /B T were somewhat greater than those obtained from arterial sampling[3] This may in part be explained by the fact that the precordial detector was recording curves that were impure in varying degree rather than a simple outflow curve as obtained by arterial sampling Nevertheless analysis of curve contours by means of the D T / B T and Cp/C_R ratios as well as the disappearance ratios of the Mayo group[23] appeared to distinguish the group with left to right shunts from the normal group Normal or abnormal ratio values obtained in a given patient however require cautious interpretation in the light of the clinical and other laboratory data It is quite possible that gross valvular insufficiency *may produce similar results* Theoretically the type of analysis utilized should sort out the slow low curves of heart failure in which normal disappearance ratios would be expected because of the proportionate prolongation of all time components Comparison of these data with those obtained in other laboratories employing similar methods and equipment should ultimately reveal the value of analysis of curve contours as an aid in the diagnosis of certain lesions

Summary

1 Comparison of precordially measured cardiac outputs with consecutive Fick determinations revealed good agreement

2 Repeated cardiac output values obtained by the isotope method agreed closely and figures for cardiac index were in the normal range for the normal group studied

3 Analysis of time components and various disappearance ratios of precordial isotope-dilution curves from normal subjects were presented and compared with results of similar analyses carried out in a group of subjects with proved left to right

shunts It appeared possible to distinguish the groups but individual curves required cautious interpretation

4 Comparison of time components and disappearance ratios in successive curves on the same subject showed that closely reproducible results were obtained

REFERENCES

1 Weinberg S L Gros G R Zipf R E Daniels D D and Murphy J P Normal response curve to exercise of relative cardiac output measured with radioiodinated serum albumin Circulation 19 590 1959
2 Shapiro O W and Sharpe A R J Precordial isotope-dilution curves in congenital heart disease simple method for the detection of intracardiac shunts Am Heart J 60 607 1960
3 Schreiner B F Lovejoy F W J and Yu P N Estimation of cardiac output from precordial dilution curves in patients with cardiopulmonary disease Circulation Res 593 1959
4 Amplatz K Marvin J Winchell I Gomez G and Adams P Simple isotope dilution technic for evaluation of congenital heart disease (Abstract) Circulation 20 663 1959
5 Huff R L Feller D D and Bogardus G M Cardiac output by body surface counting of I[131] human serum albumin J Clin Invest 33 944 1954
6 Veall N Pearson J D Hanley T and Lowe A E A method for the determination of cardiac output (preliminary report) Proceedings of the Second Radioisotope Conference Oxford 1 183 1954
7 Pritchard W H MacIntyre W J and Moir T W The determination of cardiac output by the dilution method without arterial sampling J Lab & Clin Med 46 939 1955
8 Huff R L Feller D D Judd O J and Bogardus G M Cardiac output of men and dogs measured by in vivo analysis of iodinated (I) human serum albumin Circulation Res 3 564 1955
9 MacIntyre W J Pritchard W H and Moir T W The determination of cardiac output by the dilution method without arterial sampling I Analytical concepts Circulation 18 6 1958
10 Pritchard W H MacIntyre W J and Moir T W The determination of cardiac output by the dilution method without arterial sampling II Validation of precordial recording Circulation 18 114 1956
11 Zipf R E McGuire T F Webber J M and Grove G R Determination of cardiac output by means of external monitoring of radioisotope injected intravenously Am J Clin Path 28 134 1957
12a MacIntyre W J Pritchard W H Eckstein R W and Friedell H L Determination of cardiac output by continuous recording system utilizing iodinated (I[131]) human serum albumin I Animal studies Circulation 4 552
17b Pritchard W H MacIntyre W J Schmidt W C Brofman B L and Moore D J The determination of cardiac output by continuous recording system utilizing iodinated (I[131]) human serum albumin II Clinical studies Circulation 6 572 195
13 Van der Feer Y Douma J H and Klip W Cardiac output measurement by the injection method without arterial sampling Am Heart J 56 642 1958
14 Mahoney D W Hegde B and Bauer F K Determination of cardiac output with radioactive iodinated human serum albumin clinical use (Abstract) Circulation 20 734 1959
15 Shackman R Radioactive isotope measurements of cardiac output Clin Sc 1 317 1958
16 Fosdard H A Fallers H R and Jackson R Radiogram for determination of cardiac output Comparison with Evans blue dye method U S Armed Forces M J 2 1156 1960
17 Donald K W Bishop J M Cumming G and Wade O L The effect of nursing positions on the cardiac output in man Clin Sc 12 199 1953
18 Cornell W P Braunwald E and Morrow A G External precordial scanning preliminary report of simplified method for detection of left to-right circulatory shunts Med Ann D C 29 67 1960
19 Gorten T T and Stauffer J C A study of the techniques and sources of error in the clinical applications of the external counting method of estimating cardiac output Am J M Sc 238 74 1959
20 Beierwaltes W H Johnson P C and Solari A J Clinical use of radioisotopes Philadelphia 1957 W B Saunders Company p 195
21 Brines J K Gibson J C and Kunkel P The blood volume in normal infants and children J Pediat 18 447 1941
22 Carter S A Bajec S F Yannicelli E and Wood E H Estimation of left to-right shunt from arterial dilution curves J Lab & Clin Med 55 77 1960
23 Carter S A Swan H J C and Wood E H Time and concentration components of indicator-dilution curves recorded following central injections of dye in normal human subjects Circulation 19 430 1959
24 Broadbent J C and Wood E H Indicator dilution curves in acyanotic congenital heart disease Circulation 9 890 1954
25 Korner P I and Shillingford J P The quantitative estimation of valvular incompetence by dye dilution curves Clin Sc 14 553 1955
26 Greenspan R H Lester R O Marvin J F and Amplatz K Isotope circulation studies in congenital heart disease J A M A 169 667 1959
27 Hill B Principles of medical statistics New York 1953 Oxford University Press pp 0-77 and pp 157 163
28 Mainland D Elementary medical statistics Philadelphia 19 ? W B Saunders Company pp 246 and 156

Theoretical and clinical studies of the electrocardiogram and vectorcardiogram in right ventricular enlargement

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One limitation of the electrocardiogram in the recognition of right ventricular enlargement is the difficulty of differentiating manifestations of this lesion from those of right bundle branch block. Evidence that the spatial vectorcardiogram is useful in making this differentiation has been reported, but a theoretical basis for different vectorcardiographic effects has not been established.[1] Without such a basis the evidence for differential value of the vectorcardiogram has been difficult to evaluate since there is no certain method of separating patients with enlargement and the conduction disorder from those with only enlargement or only the conduction disorder. One object of the present study was a theoretical investigation of the electrocardiographic and vectorcardiographic effects of right ventricular enlargement and of right bundle branch block. Results of this investigation indicated that these lesions may be expected to produce different vectorcardiographic manifestations and defined a theoretical basis for these differences.

Another object of this study was a theoretical investigation of the electrocardiographic and vectorcardiographic effects of different varieties of right ventricular enlargement. The effects of generalized hypertrophy, hypertrophy of the free wall, hypertrophy of the inflow and outflow tracts, and the effects of dilatation were contrasted. Results of this portion of the investigation indicated many similarities in the electrocardiographic and vectorcardiographic effects of the various types of enlargement postulated, but also indicated certain differences which seem worthy of clinical and experimental investigation to evaluate their diagnostic value.

A further object of this study was to employ some of the insights provided by the theoretical investigations in the analysis of electrocardiograms and vectorcardiograms of patients with right ventricular enlargement. The theoretical investigation suggested that the quantity described by Burger and Vaane under the term "polar vector" is a promising parameter of right ventricular enlargement, and the clinical portion of the present investigation supported this promise.

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Methods and materials

Theoretical studies The normal ventricular excitation sequence and that of experimental right bundle branch block as reported by Scher were employed in these studies[3,4] Spatial vectorcardiograms and standard electrocardiographic leads were derived from these data by means of a method which has been previously applied to ventricular excitation[8] The theoretical basis for this analysis was presented in detail in a previous publication reporting a similar analysis applied to atrial excitation[6] In this method excitation wave fronts at each of several moments on four horizontal and four frontal plane diagrams of the vertically oriented heart were considered When a wave front was interrupted by the external or internal surface of the heart the interrupted ends of the front were joined by a line and a vector was constructed perpendicular to the line and given a magnitude proportional to the length of the line multiplied by a factor proportional to the thickness of the slice from which it was derived Vectors derived from simultaneous fronts on all horizontal plane diagrams were added and their projections on horizontal (X) and anteroposterior (Z) axes were determined Similar addition of vectors from frontal plane diagrams was carried out and projection of final vectors on a vertical (Y) axis was determined The values of vectors projected on X Y and Z axes were then employed to diagram frontal and horizontal plane projections of the QRS loop and three dimensional wire models were constructed from these projections The models were oriented to approximate the anatomic position of the human heart and frontal left sagittal and horizontal plane views of the models in this new position were obtained by tracing their projections on each of these planes Standard electrocardiographic leads were derived from the projections of frontal plane loops on the sides of an equilateral triangle Detailed deviation of precordial leads from the vectorcardiograms was not attempted but vectorcardiographic features which would be likely to result in an R pattern in leads V or V were noted when they occurred

Records derived from the normal excitation sequence were considered to be controls Other records were derived from the excitation sequence reported by Scher in experimental right bundle branch block and after postulation of various degrees and types of right ventricular enlargement The types of enlargement postulated were dilatation hypertrophy of the free wall and septum and hypertrophy localized to the free wall and to the approximate regions of the inflow and outflow tracts Increases in linear dimensions of 25 50 and 100 per cent were employed for each of these situations With postulated dilatation the normal thickness of the right ventricular wall was retained With hypertrophy involving the septum the right one third of the septum was arbitrarily considered to be part of the right ventricle Direct detailed demonstration of the excitation sequence in the presence of right ventricular enlargement has not been carried out so that for the purposes of the present study this sequence was approximated with the normal activation pattern used as a guide In the case of hypertrophy the excitation fronts representing the normal activation pattern were extended into the thickened portions of the ventricular wall With dilatation it was assumed that conduction velocity was the same as in the normal heart and that the mode of delivery of excitation to the endocardial surface was similar to that in the normal heart but extended over a greater area Although there is no direct evidence that the excitation pattern postulated is the correct one the derived records had the features known to be associated with right ventricular enlargement in clinical electrocardiography

Clinical studies Fifty normal subjects and 34 patients with right ventricular enlargement were studied A medical history physical examination roentgenogram and/or fluoroscopy of the chest and conventional 12 lead electrocardiogram were obtained in each case All of the patients who were classified as having right ventricular enlargement had heart disease of a type which was expected to result in enlargement of the right ventricle and all had roentgenographic evidence of such enlargement Eight had rheumatic heart disease with mitral stenosis 16 had congenital heart disease 3 had primary pulmonary

hypertension, and 1 had cor pulmonale secondary to emphysema. The electrocardiograms of 15 patients fulfilled Milnor's criteria for right ventricular enlargement.[7] The electrocardiograms of the other 19 patients showed nonspecific abnormalities. These findings do not reflect the adequacy of Milnor's criteria for right ventricular enlargement, since a specific search was made for patients with roentgenographic evidence of enlargement but without definite electrocardiographic evidence of this lesion.

Frontal, left sagittal, and horizontal plane projections of the spatial vectorcardiogram were obtained on all subjects by means of the Frank precordial lead system. The gross features of direction of inscription, general contour, and orientation of the QRS loop in each of these planes were noted. In addition, the "polar vector" was determined. For this determination the areas of frontal, sagittal, and horizontal plane projections of the QRS loop were measured with a planimeter. For each of these QRS areas a vector was defined with a length proportional to the area, a direction perpendicular to the plane of the area, and sense such that it pointed away from the side of the QRS loop projection in which the direction of inscription was counterclockwise. These vectors were added to give the "polar vector," which was described in terms of its magnitude and the angles ψ and ϕ representing, respectively, the angle between the "polar vector" and the vertical axis and the angle between the Z axis and the projection of the "polar vector" on the horizontal plane. The special merit of this quantity in the recognition of right ventricular enlargement was suggested by the theoretical studies and will be considered further under the sections on results and discussion.

Results

Theoretical studies. Records derived after postulated right ventricular enlargement and from the excitation sequence of right bundle branch block had general characteristics known to be associated with these lesions from clinical electrocardiographic and vectorcardiographic experience. These will not be described in detail, but, as examples, right ventricular enlargement shifted the frontal plane projection of the QRS loop and the electrical axis of the ECG toward the right. Right bundle branch block yielded a QRS loop with the terminal portion located to the right of the isoelectric point, resulting in a wide, deep S wave in the derived Lead I. In addition to the commonly accepted ECG and VCG manifestations of right ventricular enlargement, the derived curves showed several effects which are less well known as manifestations of this lesion, and these will be described in greater detail.

Several ECG and VCG effects were common to all varieties of right ventricular enlargement postulated, so that the results will not be described individually for each type of enlargement. The direction of inscription and the area of the horizontal plane projection of the QRS loop seemed to be promising indices of right ventricular enlargement, and some of the results will be presented under this heading. Other results were pertinent to an explanation of the occurrence of R' patterns in Leads V_1 and V_2 and will be presented under that heading. Still other results indicated that posterior displacement of the QRS loop may sometimes be the result of right ventricular enlargement and will be described under that heading. Finally, the effects of right bundle branch block on the derived electrocardiograms and vectorcardiograms will be contrasted with the effects of enlargement. Examples of records derived from the normal excitation sequence and that of right bundle branch block and from several postulated varieties of right ventricular enlargement are shown in Fig. 1; references to this figure will be made in the following sections.

DIRECTION OF INSCRIPTION AND THE AREA OF THE HORIZONTAL PLANE PROJECTION OF THE QRS LOOP. The normal counterclockwise inscription of the QRS loop in the horizontal plane has been reported to be altered in right ventricular enlargement and to be unchanged in right bundle branch block.[1] The present study confirmed the likelihood of this alteration and provided insight into its mechanism as well as its limitations as an index of right ventricular enlargement.

The direction of inscription of a plane projection of the QRS loop depends on the

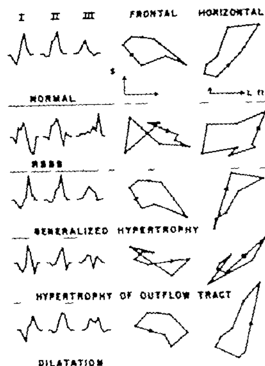


Fig *1* Electrocardiograms and vectorcardiograms derived as described in the text from the normal excitation sequence that of right bundle branch block, and after postulated generalized hypertrophy hypertrophy of the outflow tract and dilatation I each instance the effect of 50 per cent increase in linear dimensions is illustrated Note that the horizontal projection of the normal QRS loop and those of right bundle branch block and of dilatation are inscribed in counterclockwise direction whereas those of generalized hypertrophy and hypertrophy of the outflow tract are inscribed in clockwise direction Al note that localized hypertrophy of the outflow tract results in greater rightward displacement of late vectors than does generalized hypertrophy and would be more likely to be associated with an R pattern in Lead V and/or Lead V As shown in the horizontal projection dilatation result in greater anterior extension of the first half of the QRS loop than do the other postulated abnormalities

relative positions of efferent and afferent limbs The basic reason that right ventricular enlargement altered the direction of inscription in some of the derived records was that the position of the terminal portion of the afferent limb in the horizontal plane was not so markedly altered by the postulated lesion as was the position of mid temporal portions of the loop In turn the reason for less alteration of the terminal portion of the afferent limb was the relative thickness of right and left ventricular As long as the normal left ventricular wall remained thicker than the hypertrophied right ventricular wall activation in the left ventricle was still the major determinant of the position of the terminal portion of the afferent limb in the horizontal plane The initial portion of the efferent limb also remained fixed with postulated right ventricular hypertrophy since the normal excitation pattern was employed in the inner portions of ventricular walls The later portions of the efferent limb and early portions *of the afferent limb* which will be designated as the mid temporal portion of the QRS loop were altered by right ventricular enlargement As illustrated in Fig 2 these portions of the loop were displaced toward the right by right ventricular hypertrophy and this displacement together with a relatively fixed terminal portion of the loop sometimes produced clockwise rotation of the QRS loop in the horizontal plane Increasing degrees of right ventricular hypertrophy had increasing degrees of influence on the orientation of vectors in the mid temporal portions of the loop With the initial and terminal portions of the loop relatively fixed this resulted in either a smaller area of the horizontal plane loop or actual reversal of its direction of inscription The foregoing description applied to all varieties of right ventricular hypertrophy postulated Records derived after postulated hypertrophy of the outflow tract and generalized hypertrophy are shown in Fig 1 and in both instances the major area in the horizontal plane is inscribed in a clockwise direction

Right ventricular dilatation had a more complex effect Dilatation resulted in anterior displacement of early portions of the efferent limb The basis of this effect is illustrated diagrammatically in *A* and *B* of Fig 3 This displacement complicated the effects of right ventricular enlargement on QRS area in the horizontal plane since acting alone it would have produced an increase in area Thus dilatation combined with ventricular hypertrophy had less effect on the total area of the QRS loop in the horizontal plane than did the same degree of hypertrophy acting alone As shown in Fig 1 postulated dilatation with 50 per cent increase in the linear dimensions of the right ventricular cavity resulted

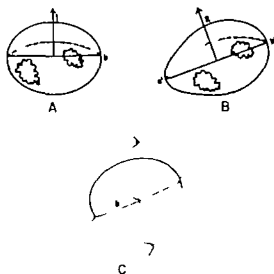


Fig 2 Diagrammatic representation of the mechanism of altered direction of inscription of the horizontal projection of the QRS loop in right ventricular enlargement *A* represents horizontal plane section of the normal heart and *B* illustrates right ventricular hypertrophy Excitation fronts are represented by the dotted lines *b* and *b* and vectors *1* and *2* by which the electrocardiographic effects of these fronts can be represented are shown Note that the effect of right ventricular enlargement has been to alter the direction of the vector toward the right *C* shows diagrammatic horizontal plane QRS loops *b* and *d* are the initial limbs and *c* is the terminal limb common to all The loop with the initial limb *a* represents the normal horizontal plane projection of the QRS loop An alteration in the position of some of the vectors making up the efferent limb in the direction which has been illustrated in *A* and *B* of this figure results in decreased area of the loop whose initial limb is labeled *b* and in reversed direction of inscription in the loop whose initial limb is labeled *d* For the purpose of clarity the effects of right ventricular hypertrophy are shown in this illustration as affecting the position of the efferent limb only As described in the text the actual effect of right ventricular enlargement on the derived QRS loops was more complex and consisted of changes in the direction of vectors as illustrated in this figure but involving only mid temporal portions of the loop.

in normal counterclockwise inscription of the QRS loop in the horizontal plane

R PATTERN IN LEAD V_1 AND/OR LEAD V_2 Although detailed derivation of precordial leads from vectorcardiograms was not carried out there were situations in which the gross features of the VCG made it likely that an R pattern in Lead V_1 and/or Lead V would have occurred These included the combination of right ventricular dilatation and generalized or localized hypertrophy of this chamber Localized hypertrophy of the outflow tract even without dilatation resulted in similar findings but with a different basis Three features of the vectorcardiograms associated with combined dilatation and hypertrophy were pertinent to the occurrence of an R pattern These were (1) forward displacement of the initial part of the efferent limb (2) small vectors with a tendency of the loop to return to the isoelectric point during its mid temporal portion and (3) rightward displacement of late vectors The forward displacement of the initial part of the efferent limb was the direct result of ventricular dilatation as has been described in the preceding section and illustrated in Fig 3 Small vectors which resulted in the location of the mid temporal portions of the loop near the isoelectric point in the horizontal plane were the result of excitation fronts essentially surrounding ventricular cavities in horizontal plane sections of the heart These wave fronts gave little external evidence of electrical activity in the horizontal plane Rightward displacement of late vectors occurred because right ventricular dilatation and a given degree of thickening of the wall represent a greater right ventricular mass than the same degree of hypertrophy alone Even though the same conduction velocity was assumed in both situations asymmetrical wave fronts approaching the right ventricular surface were longer in the case of combined dilatation and hypertrophy than in the case of hypertrophy alone This resulted in vectors relatively late in the excitation process which were directed toward the right to a greater degree than were those which were associated with hypertrophy alone Hypertrophy of the outflow tract also resulted in vectorcardiographic findings appropriate to result in an R pattern in Lead V_1 and/or Lead V but a different mechanism was responsible Early vectors were the same as those in the normal heart but later portions of the loop were now influenced by activation in the outflow tract without the simultaneous effect of activation in the remainder of the right ventricle as would have occurred with generalized right ventricular hypertrophy This had the effect of displacing a part of the afferent limb of the loop farther rightward and an

teriorly than occurred with generalized hypertrophy or hypertrophy of the inflow tract

POSTERIOR DISPLACEMENT OF THE VCG DUE TO RIGHT VENTRICULAR ENLARGEMENT Generalized hypertrophy and hypertrophy localized to the free wall or to the inflow tract displaced the loop toward the right and posteriorly Thus these forms of hypertrophy appeared less likely to result in R wave patterns in Lead V_1 and/or Lead V than did dilatation plus hypertrophy or hypertrophy localized to the outflow tract Posterior displacement of the loop was especially marked in localized enlargement of the inflow tract because activation in this portion of the hypertrophied ventricle was not balanced by simultaneous activation in the more anteriorly placed outflow tract A diagrammatic representation of the anatomic basis of these findings is shown in *C* and *D* of Fig 3 Electrocardiograms with deep S waves in precordial Leads V through V_3 have been reported in cases of right ventricular enlargement and the present investigation furnishes a possible explanation of these findings [6]

RIGHT BUNDLE BRANCH BLOCK Electrocardiograms and vectorcardiograms derived from the excitation sequence in experimental right bundle branch block had the features known to be associated with this conduction disorder in patients The terminal portion of the QRS loop was inscribed slowly and was located to the right of the isoelectric point This portion of the loop resulted in a wide deep S wave in the derived Lead I and was appropriate to result in an R wave in Lead V and/or Lead V as occurs in patients with right bundle branch block The direction of inscription of the horizontal plane projection of the QRS loop was counterclockwise Only the terminal portion of the afferent limb was grossly altered by this conduction disorder The normal left septal excitation directed first rightward and anteriorly and later left ventricular activation directed leftward and posteriorly resulted in a horizontal plane projection of the QRS loop inscribed in the normal counterclockwise direction

Clinical studies As expected from previous studies a variety of electrocardiographic and vectorcardiographic findings were encountered in patients with right ventricular enlargement These findings included various degrees of right axis deviation rightward deviation of the QRS loop large R waves or R patterns in Lead V_1 and/or Lead V and nonspecific abnormalities of the S T segments and T waves The merits and limitations of these findings as diagnostic evidence of right ventricular enlargement have been considered in many reports and will not be described in detail

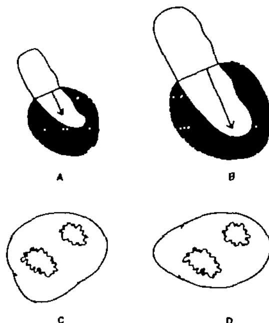


Fig 3 *A* and *B* illustrate diagrammatically the mechanism of anterior displacement of early portions of the QRS loop by right ventricular dilatation *A* represents the right ventricular cavity viewed in the horizontal plane with the adjacent shaded area representing activated right ventricular muscle The anteriorly directed vector by which this excitation moment can be represented is shown perpendicular to line connecting the interrupted edges of the excitation front In *B* a similar diagram of dilated right ventricular cavity is illustrated Excitation has been extended over a greater portion of the endocardial surface and a larger anteriorly directed vector is necessary to represent this excitation moment The anatomic basis for different ECG and VCG effects of enlargement of the outflow and inflow tracts is illustrated in *C* and *D* In these diagrammatic horizontal plane sections of the heart the lower edge represents the anterior wall *C* illustrates hypertrophy of the outflow tract Hypertrophy of the inflow tract is shown in *D* Excitation front extending into the more anteriorly placed outflow tract resulted in greater anterior displacement of vector by which these fronts could be represented

The theoretical portion of this study provided several insights into the possible mechanism of some of the ECG and VCG manifestations of right ventricular enlargement and suggested certain parameters which may be useful in the differential diagnosis of the type of enlargement The differential value of these parameters could not be evaluated in the present clinical study since pathologic demonstration of the type of enlargement present would be necessary for such an evaluation One method of analysis of the VCG which the theoretical studies suggested as promising for the recognition of right ventricular hypertrophy was appropriate to the present study and was evaluated in detail The theoretical finding that hypertrophy sometimes alter the direction of inscription of the QRS in the horizontal plane and at other times decreases the area of this loop without altering the direction of inscription suggested that a quantitative parameter incorporating both direction of inscription and area of the loop might be useful in the recognition of right ventricular hypertrophy The polar vector is a quantity with these characteristics and was calculated as described in the section on methods In this series there was no significant difference between the normal records and those of patients with right ventricular enlargement in the mean values of the polar vector magnitude and the angle ϕ although there was a greater range of variation of both calculated from records of patients with enlargement The values of ψ however were significantly different in the right ventricular enlargement and normal groups In the normal group the average value of ψ was 36 degrees and in the records of patients with enlargement the value was 97 degrees The range of variation in the normal records was 13 to 2 degrees (standard deviation of 13 degrees) with all but two values being less than 55 degrees In the right ventricular enlargement group the range was 33 to 161 degrees (standard deviation of 35 degrees) with all but two records having a value greater than 55 degrees These records included those from 19 patients whose electrocardiograms did not fulfill Milnor's criteria for right ventricular enlargement. When these latter patients were considered as a group there was still a highly significant difference between the values of ψ for this group and the values for the normal group

Discussion

It should be emphasized that the theoretical studies reported were carried out only to furnish insight into the possible mechanism of electrocardiographic and vectorcardiographic manifestations of right ventricular enlargement Evaluation of the usefulness of specific parameters in the recognition of various types of right ventricular enlargement will require combined clinical and pathologic studies The clinical portion of the present investigation supports the usefulness of one parameter namely the polar vector as an index of right ventricular hypertrophy This quantity differed significantly between normal records and those of patients with right ventricular enlargement including several patients without currently accepted electrocardiographic evidence of that lesion

The theoretical studies had definite limitations and necessitated several simplifying assumptions These include consideration of excitation at only a limited number of moments and at a limited number of anatomic levels They also include the assumptions that standard ECG leads represent projections of the frontal plane loop on the sides of an equilateral triangle and that vectorcardiograms represent projections on a perfect orthogonal lead system It was also necessary to postulate the excitation sequence in enlarged portions of the right ventricle since direct studies of the excitation order in this situation have not been carried out Despite these limitations and assumptions the theoretical approach appeared to be worth while since it is extremely difficult to be certain that right ventricular enlargement is not associated with a conduction disorder in either experimental or clinical situations In this study it was possible to postulate ventricular enlargement and retain the normal excitation sequence and to contrast the effects of this lesion alone with those of right bundle branch block

It was recognized that the insights provided by the theoretical studies require clinical and pathologic evaluation The results of the theoretical studies correlated

well with the limited clinical observations in the present study. They provided a theoretical basis for the finding that the normal direction of inscription of the QRS loop in the horizontal plane is sometimes altered by right ventricular enlargement. This alteration was the result of disproportionate effect of hypertrophy on the position of the mid temporal portion of the loop as compared to the initial and terminal portions. The studies also indicated that slight or moderate degrees of hypertrophy might be expected to decrease the area of the horizontal plane projection of the QRS loop without actually altering the direction of inscription. This was also the result of greater effect on the position of the mid temporal portion of the loop. These findings made it appear that the "polar vector" determined from the area of plane projections of the loop and its direction of inscription might be a valuable index of right ventricular enlargement and the clinical portion of this study supported this possibility.

The theoretical studies also suggested several parameters which may be useful in the differential diagnosis of the type of enlargement present. The possible value of these could not be evaluated in the clinical portion of this study since this would require pathologic demonstration of the type of enlargement present, but the features with possible differential value were as follows: (1) Clockwise direction of inscription or decreased area of the horizontal plane projection of the QRS loop was a manifestation of all types of enlargement studied but was less marked with dilatation than with hypertrophy of the right ventricle. (2) The amount of anterior extension of the initial limb of the QRS loop was increased by dilatation but not by hypertrophy. (3) Vectorcardiographic features likely to be associated with an R pattern in Lead V₁ and/or Lead V₃ occurred with combined dilatation and hypertrophy of all varieties studied and with isolated hypertrophy of the outflow tract but not with other types of hypertrophy. (4) Posterior displacement of the QRS loop likely to be associated with deep S waves in the precordial leads was especially marked with isolated hypertrophy of the right ventricular inflow tract. Further clinical study, together with pathologic demonstration of the variety of enlargement present, will be necessary to evaluate the possible differential diagnostic value of these findings.

Summary

A theoretical study in which the electrocardiographic and vectorcardiographic effects of right bundle branch block and of several varieties of right ventricular enlargement were examined was carried out. The basis of this study was derivation of electrocardiograms and vectorcardiograms from the ventricular excitation sequence. Results of the study provided a theoretical basis for the observation that right ventricular enlargement may alter the direction of inscription of the QRS loop in the horizontal plane. Results also indicated that right ventricular enlargement may decrease the area of projection of the QRS loop in the horizontal plane without changing the direction of inscription. On the basis of these results a quantitative parameter, the "polar vector," based on the area of plane projections of the VCG and their direction of inscription was examined in records from a group of normal subjects and records from patients with right ventricular enlargement. Results of this clinical study showed a significant difference in the orientation of this vector in records from normal subjects and those with right ventricular enlargement. The group studied included several patients whose conventional electrocardiograms were not diagnostic of right ventricular enlargement.

The theoretical study also suggested several ECG and VCG features of possible value for identifying specific varieties of right ventricular enlargement. These have not been evaluated clinically since this will require demonstration of the type of enlargement present.

REFERENCES

1. Grishman, A., and Scherlis, L.: Spatial vectorcardiography, Philadelphia, 195[illegible], W. B. Saunders Company.
2. Burger, H. C., and Vaane, J. P.: A criterion characterizing the orientation of vectorcardiogram in space, Am. Heart J. 56:29, 1958.
3. Scher, A. M., and Young, A. C.: The pathway of ventricular depolarization in the dog, Circulation Res. 4:461, 1956.
4. Erickson, P. V., Scher, A. M., and Becker

R A \entricular excitation and experimental bundle branch block Circulation Res 5 5 1957
5 J cobson E D Ru h S Zmberg S and Abildskov J A The effect of infarction on magnitude and orientation of electrical events in the heart Am Heart J 58 863 19 9
6 Abildskov J A Barnes T G and Huey B L Studies of normal and ectopic atrial excitation Am Heart J 52 496 1956
7 M lnor W R The electrocardiogram and vectorcardiogram in right entricular hypertrophy and right bundle branch block Circulation 16 348 1957
8 Shubin H and Levinson D C The deep S w in Leads V V and V in right entricular hypertrophy Circulation 18 410 1958

Toxicity of Coomassie blue

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Coomassie blue has recently been advocated as a suitable dye for indicator dilution studies It is especially suitable for repeated injection since the level in blood falls much more rapidly than with Evans blue and the subject does not remain blue for many days Preliminary animal studies showed that Coomassie blue was even less toxic than was Evans blue and initial reports of its use in man confirmed the absence of toxicity in doses of 20 to 1 000 mg one subject received 2 000 mg in 24 hours without ill effect

We wish to report here 3 severe pyrogenic reactions in 2 healthy people (ourselves) who received large amounts of Coomassie blue on 3 separate occasions to verify the response characteristics of an ear oximeter

a Injection of 450 mg in 7 doses was given over a 5 hour period 300 mg were given in the last 2 hours

b Injections of 40 48 78 168 188 and 276 mg were given at 9 minute intervals a total of 798 mg was given in 54 minutes and the maximum blood level reached was 99 5 mg per liter

c Injections of 40 36 72 161 186 194 and 235 mg of dye were given at 9 minute intervals a total of 924 mg was given in 63 minutes and the maximum blood level reached was 138 5 mg per liter

On each occasion there was a period of 2 to 3 hours of well being after the last injection This was followed by vague malaise which lasted 10 to 15 minutes and then by rigors with fever up to 104 F (40 C) marked hyperesthesia of skin and muscle nausea and vomiting and (once) diarrhea Blue dye was noted in the vomitus and diarrhea fluid this is in keeping with its known elimination in the bile[1] No pain in the joints effusions rash bronchospasm or abdominal pains were noted The fever and symptoms slowly subsided over the course of 5 or 6 hours—once after 600 mg of acetylsalicylic acid per os and twice after 50 mg of diphenhydramine hydrochloride (Benadryl) intramuscularly we do not know whether this treatment altered the natural course of the illness Minor episodes of sweating with low grade fever occurred for 2 or 3 days more but no other sequelae were noted Blood cultures taken during a rigor were sterile each time and the total and differential leukocyte counts were normal

Since that time the same subjects have received smaller amounts of dye without ill

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effect the maximum blood levels however have been much lower than during these reactions On one occasion 8 injections of 54 mg were given over 8 hours with a maximum blood level of 8 9 mg per liter Many other subjects have had 6 injections of 50 mg over 4 to 5 hours with no adverse reactions

The cause of the pyrogenic reaction has not yet been found it is clearly related to high blood and/or tissue levels No evidence of particulate matter was detected on microscopy of plasma containing 200 mg per liter of dye nor was any detected in the dye itself by bacterial filters The clinical course is unlike that due to a bacterial pyrogen[3] The unusual latent period must be of significance and it should be noted that after accidental perivenous injection of the dye severe pain ensued after a time interval of similar duration Further studies into the mechanism are being made by workers at the Imperial Chemical Industries in the United Kingdom

It should be stressed that low doses of Coomassie blue can be used safely within this limitation it remains a valuable agent for studies involving frequent indicator dilution curves

REFERENCES

1 Taylor S H and Thorp J M Properties and biological behavior of Coomassie blue Brit Heart J 21 492 1959
2 Taylor S H and Shillingford J P Clinical application of Coomassie blue Brit Heart J 21 497 1959
3 Bennett I L Jr and Beeson P B The properties and biological effects of bacterial pyrogens Medicine 29 365 1950
4 Thorp J M Personal communication 1960

Vectorcardiographic deflections obtained with various reference systems in cadavers

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Many systems of electrode placement have been proposed and are being used for spatial vectorcardiography. Some of these are based on carefully controlled experiments on torso models. This report is concerned with results of similar experiments on fresh cadavers through the use of some popular vectorcardiographic reference systems.

Methods

Needle electrodes, insulated except at the tips, were assembled in a Lucite base as shown in Fig. 1. The electrodes were inserted through the chest into the heart of the fresh cadaver (2 to 6 hours post mortem) and appropriately supplied with 20-cycle current. These electrodes constituted artificial dipoles which were orthogonally oriented horizontally, vertically, and front to back, and at 45° angles to both frontal and sagittal planes (pointing anteriorly, inferiorly, and toward the left of the body). Separate similar electrode arrangements without fixation to a Lucite base were also inserted directly into the exposed heart, and then the chest was closed for the study. Individual lead boxes permitted rapid transfer of the amplifiers and cathode ray tubes for frontal and left sagittal display from electrodes located

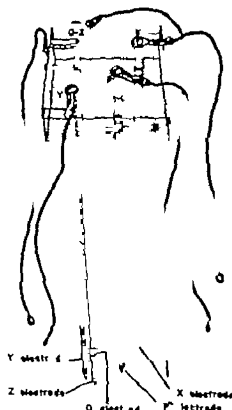


Fig. 1. The electrodes used for the pseudo-dipoles which were inserted into the heart through the anterior chest wall of 15 intact cadavers.

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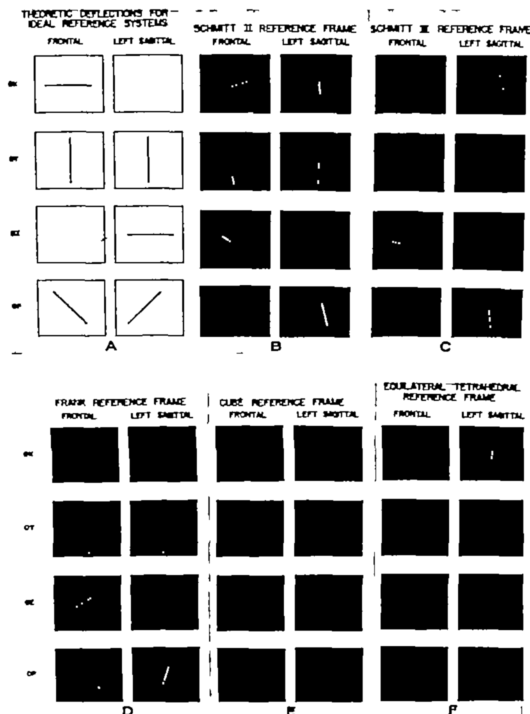


Fig 2 A The theoretical deflections that would be obtained in the frontal and left sagittal plane projections for ideal reference systems and dipole orientation OX is parallel to the horizontal in the frontal plane OY is parallel to the vertical in the frontal plane OZ is perpendicular to the frontal plane OP is at an angle of 45 to the frontal and sagittal planes *B* Typical recording obtained from cadaver for the frontal and left sagittal plane projections with the Schmitt II method of electrode placement The recordings shown [illegible] *B* through *F* were obtained for the same cadaver and the same artificial dipoles *C* Typical recording obtained from the cadaver for the frontal and left sagittal plane projections with the Schmitt III method of electrode placement *D* Typical recording obtained from the cadaver for the frontal and left sagittal plane projections with the Frank method of electrode placement *E* Typical recording obtained from the cadaver for the frontal and left sagittal plane projections with the cube method of electrode placement *F* Typical recording obtained from the cadaver for the frontal and left sagittal plane projections with the equilateral tetrahedral method of electrode placement

according to the Schmitt II,[1] Schmitt III,[1] simplified Frank,[2] cube,[3] and Wilson's equilateral tetrahedral[4] systems. The Burger system was not studied because of the difficulty of adapting the equipment to that system. Time limitation on each experiment imposed by the pathologist also restricted the number of systems which could be studied on each body. Two dimensional roentgenograms and subsequent opening of the chest permitted determination of the actual spatial position of the dipole electrodes in the heart. In each experiment the recommended amplifier standardization was employed and the dipole current was constant.

Results

Experiments were performed on 15 cadavers. If penetration of the heart muscle by the dipole electrodes was not satisfactorily obtained, the observations were discarded. The results obtained from the various satisfactory experiments for the respective reference systems studied are typified by Fig. 2, B–I. The theoretically correct vectorcardiographic directions are shown in Fig. 2,A.

Discussion

The difficulty of achieving truly symmetrical electrode placement in this experiment is realized. Variable contact resistance around the periphery of the electrodes and improper implantation of the electrodes in the heart muscle are among the technical factors which may have modified the effective dipole direction from the physical direction between the electrodes. In any case, all of the chosen vectorcardiographic systems were tested with the same pseudo dipoles. The variations in recorded directions and magnitudes for presumably the same views of the dipoles indicate that none of the systems tested were completely satisfactory.

The pseudo-dipole electrodes in the heart of the cadavers probably were not spatially oriented as precisely as desired, but once they were in place, they were used for all the reference systems investigated. Thus, if each reference system were ideal, the recorded deflections would have been the same for all systems.

Although the fresh cadaver is different from a living man, such an experimental model resembles the living intact man more closely than does an artificial torso model.

Summary

A study of artificially applied dipoles in the heart of fresh cadavers clearly showed that some systems of electrode placement employed for spatial vectorcardiography are far from perfect.

REFERENCES

1. Schmitt, O. H., and Simonson, E.: Symposium on electrocardiography and vectorcardiography: the present status of vectorcardiography, A.M.A. Arch. Int. Med. 96:574, 1955.
2. Frank, E.: An accurate, clinically practical system for spatial vectorcardiography, Circulation 13:737, 1956.
3. Grishman, A., and Scherlis, L.: Spatial vectorcardiography, Philadelphia, 1952, W. B. Saunders Company.
4. Burch, G. E., Abildskov, J. A., and Cronvich, J. A.: Spatial vectorcardiography, Philadelphia, 1953, Lea & Febiger.

Precordial low frequency displacements of the thoracic wall
Method of recording and registration

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The recording and registration of low frequency precordial movements of the chest wall caused by cardiac action have become the focus of increasing attention in the past few decades. In this connection, we may refer to publications by Johnston and Overy, in which is presented a survey of results obtained up to 1951 with their interpretation.

Continuing this line of investigation, Eddleman, Luisada, Groom and Elliott[11] with their respective co-workers have developed recording methods which have contributed to our knowledge of precordial movements of the chest wall. For this purpose Eddleman made use of the fact that mechanical fluctuation in pressure can be piezoelectrically converted into electrical signals. Luisada recorded precordial movements of the chest wall with the aid of a contact crystal microphone. Groom used the electronic pick up RCA 5 34—the triode with the moving anode. Elliott used the accelerometer based on the principle of electrocapillarity.

For the same purpose we have used the Philips displacement meter and transducer based on the principle of the differential transformer.

Method

If mechanical quantities are measured by electrical methods, then the apparatus required can be divided into two parts, i.e. (a) the transducer with which the mechanical quantity is converted into an electrical quantity, and (b) the measuring apparatus with which the electrical quantity is amplified and measured.

The transducer. The transducer PR 9310/01 is an instrument with a length of 5.3 cm and a diameter of 2.3 cm (transverse section shown in Fig. 1). It consists of a steel casing (*A*) with a copper lining (*B*) from which a needle (*K*) protrudes. We fixed a globule of resin (*E*) with a diameter of 1 mm onto the end of this protruding needle. The center of the needle contains a small ferromagnetic core (*H*). Both the needle and the core are movable in axial direction in a tube (not magnetizable) within the steel casing) on which one primary (*C*) and two secondary coils (*G*) have been mounted.

The axial movement of the core of the measuring needle results in a change in the coupling of each of the two secondary coils with the primary coil; as a result the voltages induced in the secondary coils

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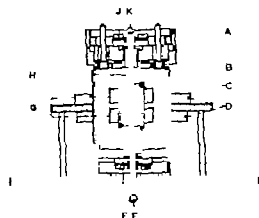


Fig. 1 Transverse section of the transducer and plastic holder (ϕ6 cm.)

are opposed. The ensuing difference in voltage can be determined with the aid of a suitable measuring apparatus connected with the transducer by means of a measuring cable 5 M. in length.

The coil system of the transducer is electrically screened off by means of the copper lining inside the steel casing. The induced voltages, therefore, are not influenced either by the metal holder into which the instrument may be built or by static fields in the vicinity.

The primary coil is fed stabilized alternating current (2.75 volts effective at 30 Ma. 4,000 Herz.).

With the aid of adjusting nuts (*D*) the entire system was mounted in an adjustable plastic holder (ϕ 6 cm.) which can be attached to the patient by means of a rubber band so that the measuring needle can be applied to any desired site on the thorax. In this way the investigator's interference with registration as well as the influence of respiration are avoided, as are also minor displacements of the patient relative to a transducer not attached to the patient. The displacement of the rim of the holder is small in comparison to the displacement of the probe.

The mass of the moving system amounts to 1 gram, and this implies that the influence on the object to be measured is inconsiderable. The measuring needle of the transducer is subject to outward pressure exerted by bearing springs (*F J*) with a force which amounts to about 2×10^4 dynes in the central position. The spring rigidity is 15×10^4 dynes per centimeter. During use the measuring needle must not be subjected to transverse stress, i.e., stress perpendicular to the longitudinal axis.

The maximal deflection, i.e., the permissible deflection longitudinally to either side

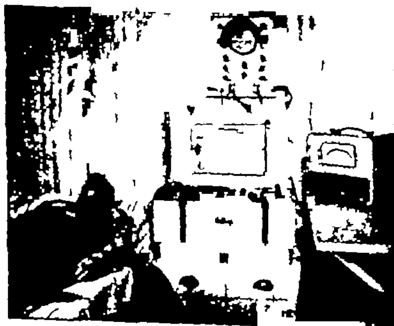


Fig. 2. *Left*: Transducer fixed on the patient. *Center*: Hellige recorder and the cathode ray tube. *Right*: M[illegible]ng apparatus.

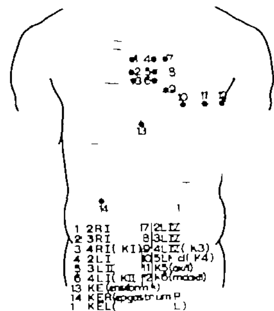


Fig 3 See text

of the central position of the measuring needle is 1 mm Overloading of the measuring apparatus occurs after larger displacements of the chest wall The apparatus is capable of measuring independently vibrations ranging from frequency 0 cycles per second to frequency 70 cycles per second (independent of amplitude) a reproducible and proportionate recording of the displacement of the chest wall is thus ensured The sensitivity is 0 25 mv /μm

It should be pointed out that the output voltage emitted is proportionate to the displacement instead of to the velocity as in the case of electromagnetic and electrodynamic recorders

The measuring apparatus The measuring bridge which can be regarded as a bridge of wheatstone is the most important part of the measuring apparatus (PR 9300)[*] This bridge combined with the transducer described in the previous section makes it possible to measure the displacements of the measuring needle

It is possible to adjust the apparatus to the following six measuring ranges which differ by a factor of 3 from +3 to −3 μm +10 to −10 μm +30 to −30 μm +100 to −100 μm +300 to −300 μm +1 000 to −1 000 μm

The values for slow fluctuations of the chest wall e g due to respiration can be read directly from a dial instrument (continuous current microamperemeter with 500 microamperes at full dial deflection) In our experiments this instrument was used only for orientation as to measuring limits

After adjustment observations were made with the aid of a cathode ray tube for visual evaluation and the recording with a four channel photographic Hellige apparatus The output of the measuring apparatus it was found could be readily adapted to the final stage of the above mentioned Hellige apparatus Recordings were made synchronously with heart sounds and electrocardiographic findings

If desirable a segment of the displacement curve with high sensitivity can be studied in detail while the remainder of the curve is overloaded

Application to the patient The above described apparatus is set up and the transducer attached to the chest of the

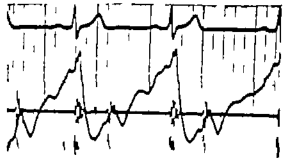


Fig 4 Kinetocardiogram (2R1) = K[II] Measuring range +10 μm t −10 μm ECG Lead II Phonocardiogram Apical sound Speed of paper 50 mm per second

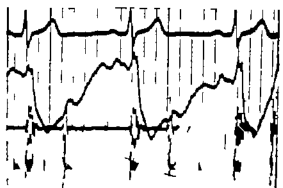


Fig 5 Kinetocardiogram (3R1) = K Measuring range FCG phonocardiogram and paper speed are the same as for Fig 4

[*] PR 9300 — Serial number of Philips Electronics.

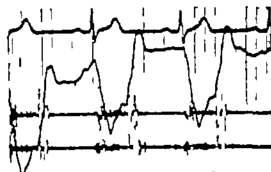


Fig 6 Kinetocardiogram (4R1) = K Phonocardiogram Sounds 2L1 Measuring range ECG and paper speed are the same as for Fig 4

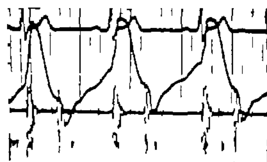


Fig 7 Kinetocardiogram (2L1) = K_{III} Measuring range $+30$ μm to -30 μm ECG Lead II Phonocardiogram Apical sounds Speed of paper 50 mm per second

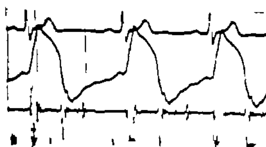


Fig 8 Kinetocardiogram (3L1) = K_{III} Measuring range ECG phonocardiogram and paper speed are the same as for Fig 7

subject under examination in the manner demonstrated in Fig 2 It is ascertained that the measuring needle of the transducer is localized at the exact site on the chest wall at which precordial movements are to be measured the transducer with the measuring needle can be shifted in the holder (by means of a fine pitched screw thread) in such a way that the measuring needle itself is in the central position perpendicular to the chest wall This last point can be checked against the position of the dial on the scale of the measuring apparatus At the same time the electrodes for the electrocardiogram are applied and in a number of cases for reference heart sounds are simultaneously recorded elsewhere on the chest wall

It must be borne in mind that the mass of the heart sound microphone may influence recording when an attempt is made to derive both phenomena too close together with the measuring apparatus in a sensitive measuring position

We carried out recordings with the patient in deep expiration holding his breath

Results

Fig 3 shows the sites on the precordium and elsewhere at which we recorded precordial movements or their derivations

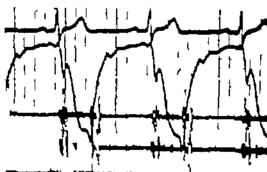


Fig 9 Kinetocardiogram (4L1) = K_{III} Measuring range $+30$ μm to -30 μm ECG Lead II Phonocardiogram Sounds L1 Speed of paper 50 mm per second

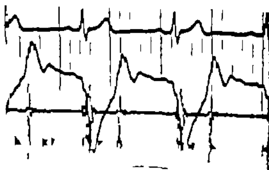


Fig 10 Kinetocardiogram (2L4) = K_4 Measuring range ECG phonocardiogram and paper speed are the same as for Fig 7

Wherever these sites corresponded with those also used by Eddleman we inserted the Eddleman designations of K (kinetocardiogram) with corresponding numeral.

Obviously, the small integrating surface of the transducer makes it possible to enlarge the field of derivation points. It will and explore the entire precordium in this manner which ensures excellent curves illustrating the course.



Fig. *11*. Kinetocardiogram (3L4) = K. Curve obtained above ictus of right ventricle. Measuring range +30 μm to −30 μm. ECG Lead II. Phonocardiogram: Sounds 2R1. Speed of paper 50 mm per second.

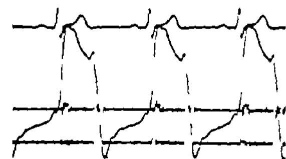


Fig. *12*. Kinetocardiogram. Left ictus, dorsal recumbent position. Measuring range +50 μm to −50 μm. ECG Lead II. Phonocardiogram 2R1. Speed of paper 50 mm per second.

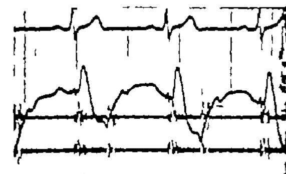


Fig. *13*. Kinetocardiogram K_{14}. Measuring range, ECG, phonocardiogram, and paper speed are the same as for Fig. 11.

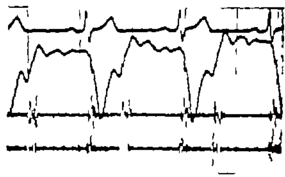


Fig. *14*. Kinetocardiogram K_{14}. Measuring range +10 μm to −10 μm. ECG Lead II. Phonocardiogram: Sound 2L1. Speed of paper 50 mm per second.

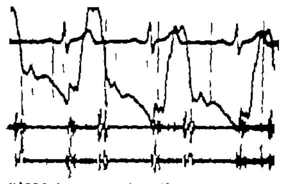


Fig. *15*. Kinetocardiogram K ensiform. Measuring range, ECG, phonocardiogram, and paper speed are the same as for Fig. 14.

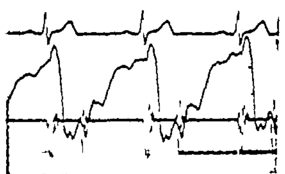


Fig. *16*. Kinetocardiogram. Mid-clavicular 1R epigastrium. Measuring range, ECG, phonocardiogram, and paper speed are the same as for Fig. 14.

Figs 4 through 16 present a few results obtained by this method of registration in a 13 year-old male patient

A detailed discussion or explanation of the illustrations is not within the scope of this paper

Summary

1 A description is given of a new method of recording precordial movements of the chest wall with illustrations depicting the apparatus and the mode of application to the subject to be examined A number of curves obtained by this method are presented in addition

2 The authors believe that the new method offers the following advantages over conventional recording methods (a) small integrating surface of the transducer as a result of which precordial displacements of the chest wall are locally measured whereas other transducers measure a contribution from several precordial sites (b) proportional and reproducible recording of precordial displacements caused by the heart action (c) instant registration frequency range and high sensitivity because of the physical characteristics of the transducer and the measuring apparatus

3 Results and interpretations obtained from hearts with a normal and a pathophysiologic function will be presented in a subsequent publication

REFERENCES

1 Crehore A Study of tracings from region near apex of heart J Exper Med 14 351 1911
2 Weitz W Über die Kardiographie am gesunden Herz mit dem Frankschen Apparat Über die Kardiographie des pathologischen Herzens mit dem Frankschen Apparat Deutsch Arch klin Med 124 134 and 155 1917
3 Wiggers C J Circulation in health and disease Philadelphia 1923 Lea & Febiger
4 Dressler W Die Brustwandpulsationen al Symptome on Herz und Gefässkrankheiten Vienna 1933 Verlag Wilhelm Maudrich
5 Rappaport M B and Sprague H The graphic registration of the normal heart sounds Am Heart J 23 591 1942
6 Johnston F D and Overy D C Vibration of low frequency over the precordium Circulation 3 579 19 1
7 Luisada A and Magri G The low frequency tracings of the precordium and epigastrium in normal subjects and cardiac patients Am Heart J 44 545 1952
8 Eddleman E E J Willis K Reeves T J and Harrison T R The kinetocardiogram Method of recording precordial movements Circulation 8 69 1953
9 Eddleman E E J Willis K Christianson L Pierce J R and Walker R R The kinetocardiogram The normal configuration and amplitude Circulation 8 370 1953
10 Eddleman E E J and Willis K The kinetocardiogram The distribution of forces over the anterior chest Circulation 8 569 1953
11 Groom D and Boone J A The recording of heart sounds and vibration II The application of an electronic pick up in the graphic recording of subaudible and audible frequencies Exper Med & Surg 14 255 1956
12 Eddleman E E J Hefner L Reeves T J and Harrison T R Movements and forces of the human heart I The genesis of the apical impulses Arch I ternat Med 99 401 19 7

Arterial volume and pressure pulse contours in the young human subject

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The dynamics of blood flow in peripheral arteries have been a subject of intense study since the original publication of Poiseuille and Frank. Otto Frank's main interest centered on the problem of propagation of pressure waves in elastic tubes, but he also recognized the problem of propagation of wall vibrations as independent of that of pressure transmission. Subsequently in the voluminous literature on the transmission of pulse waves, definite distinction has not always been made between volume pulses and pressure pulses, and recordings of changes in vessel diameter have been used to discuss the properties of pressure pulses. Although under normal conditions local increase in arterial capacity is a reliable index of the degree of elevation in intraluminal pressure, under conditions of vasoconstriction or vasodilatation this may not be so; furthermore, the pressure with which volume-sensing elements are applied against the artery determines largely the size and contour of the recorded pulses without much affecting the intra-arterial pressure.[2,3]

So far volume pulses from arterial trunks in vivo correlated directly with pressure pulses have been obtained only in animal experiments, either through a mercury in rubber strain gauge[4] or through a differential transformer attached indirectly to the vessel. Circumference has been plotted against pressure either continuously on the Y and X axes of a cathode ray tube[4] or by feeding information received onto a tape recorder and performing automatic analog or digital computer analysis of the data.

Electrical impedance plethysmography offers the possibility of recording volumetric changes of arterial trunks in situ in human beings with little discomfort to the subject. We have used an instantaneously subtracting amplifier and recorded the scalar difference of pressure minus impedance (volume) pulses; details of brachial arterial capacity versus pressure have been studied in this way in the young human subject.

Subjects and methods

Ten healthy volunteer male students aged 18 to 24 years were studied in a room with average temperature of 78° to 84° F. The subjects were examined in recumbency and the left arm was positioned at the cardiac zero pressure level by the use of a soft arm support. The left brachial artery at the elbow was punctured with a Cournand needle which was connected with a 10 cm. or 30 cm. long *rigid* polyethylene catheter (external diameter 3 mm.

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internal diameter 2 mm) to a Statham P23AA gauge The gauge output was fed into a pressure amplifier of an Electronics for Medicine recorder The needle was flushed repeatedly with heparinized saline solution during the course of each experiment natural frequency response of the pressure pick up system was 35 and 50 cycles per second with the longer and shorter connecting tubes respectively In 3 further male volunteers the brachial and/or femoral artery was entered with a 15 gauge needle a 25 cm long PL 90 polyethylene catheter was introduced through it into the artery and the needle removed thereafter the polyethylene catheter was directly connected with the strain gauge

Impedance changes of the artery were measured by means of a two electrode system and a transistorized impedance plethysmograph this unit operates on a carrier frequency of 30 kilocycles and the current flowing through the skin and subcutaneous electrodes is approximately 2 milliamperes (this is not perceptible by the subjects) Time constant of the impedance amplifier plus connected ECG channel of recorder was 1 5 seconds the amplifier of the recorder channel had a frequency response flat from 0 1 to 100 cycles for second and a cut off rate of 6 decibles per octave at each end

The Cournand needle or the tip of the polyethylene catheter was used as one electrode the other electrode was either a one inch round lead disc placed on the skin (with ECG standard paste and adhesive tape) over the tip of the needle or catheter or a subcutaneously inserted 21 gauge stainless steel needle (¾ inch) coated with insulating material except for its tip The needle was inserted parallelly and as close to the artery and tip of the polyethylene catheter or Cournand needle as possible The delay of the entire pressure pick up system with respect to the impedance system was 0 0036 second this delay and the frequency responses of the two recording systems were observed from transient oscillations with the needle catheter and electrodes connected to a saline filled rubber tube

Manufactured by Park Electronics Lab Wheel Ct Aloha, Ore

The impedance pulses were calibrated by adding into the circuit a pure resistance of 0 1 ohm this resistance was also used to determine the time constant of the unit and connected amplifiers in all records an increased conductance (decreased resistivity) is indicated by an upward deflection

The impedance pulse and the pressure pulse were initially compared by connecting them with the Y and X axes of a second cathode ray tube Since no easy method for detailed study of their composite curve was available in the majority of experiments the height of the impedance pulse was adjusted to equal exactly that of the pressure pulse then pressure pulse and impedance (volume) pulse were fed respectively into the plus and minus sections of a subtracting DC amplifier The scalar difference of the two pulses (pressure minus volume) was simultaneously recorded along with the pulses themselves and the electrocardiographic Lead II on photographic paper at a speed of 84 mm per second This enabled us to compare fine differences of latent periods and contour details in these amplitude-equalized pulses which could not be done easily by simple simultaneous recording of the two pulses

A short period of hypertension was obtained by voluntary breath holding for 30 to 60 seconds or with the cold pressor test Inhalation of amyl nitrite for a few seconds was used to briefly lower the blood pressure Recordings were taken usually at the points of maximal change in blood pressure

Results

1 Relative delay of the pressure pulse In most cases the foot of the pressure pulse trailed that of the impedance pulse obtained at the same point by a fairly constant interval in each individual this was true when either the skin or subcutaneous electrode was used for the impedance pulse This delay is evident in the tracings of the subtraction curve of the two pulses by an initial *slow* downward movement from its end diastolic base line (Figs 1 2 and 3) The net mean temporal delay (recorded lag minus lag of the pressure system) of the foot of the pressure pulse with respect to that of the volume pul

the brachial level was 0 0104 ± 0 0127* second in these subjects with a mean pulse wave transmission velocity of 7 meters per second the distance between the front of the volume pulse and that of the pressure pulse must be about 7 cm at the level of the elbow Attempts at determining this distance by introducing a catheter upstream until the fronts of the two pulses coincided were successful only once in the femoral artery (see Fig 1 lower section) The distance between volume recording and pressure recording devices was 3 5 cm The pressure pulse delay previously described by Heyman[7] who used another method for recording external pulses varies with vasomotion vasoconstriction decreases it and vasodilatation increases it by 5 to 8 *thousandths of a second (see Fig 3)* during hypertensive periods the rise in pressure may even precede the rise in volume as would occur in a rigid tube expanding only after a certain rise in pressure

2 Differences between volume and pressure pulse contour Despite the delay of its front the pressure pulse rises faster than does the volume pulse this is evident in the subtraction curve of the two pulses (Figs 1 and 2) by its sudden reversal to the zero level or above it after the early negative phase Thus the crest of pressure is reached before that of volume

The net mean time at which the subtraction curve reversed its course from negative to positive (equal rates of rise in volume and rise in pressure) was 0 021 ± 0 020 second the net mean time at which the subtraction curve returned to the base line i e the deflections of volume and pressure became equal was 0 035 ± 0 027 second for the entire group of persons

The volume systolic plateau is a rule lasts longer than the pressure systolic plateau the pressure pulse has at this site a definitely peripheral character with a narrow plateau followed by a deep notch[8,9] As a consequence the subtraction curve becomes negative again during the remainder of systole and approaches the zero line of difference at about the dicrotic notch At this point also the volume curve lags behind the pressure curve so that the over all duration of systole in the volume pulse exceeds by 0 04 to 0 06 second that in the pressure pulse more than half of this is due to the relative lag of the dicrotic notch in the volume pulse

In diastole the rebound dicrotic wave of the volume pulse is also constantly

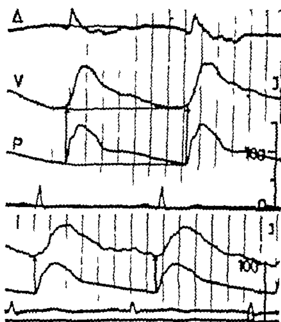


Fig 1 Upper section Volume pulse (V) and pressure pulse (P) of the left femoral artery and net instantaneous difference between them (Δ) volume pulse being subtracted from the pressure pulse Electrocardiographic lead II coincides with the pressure base line The pressure pulse is obtained from a 25 cm long PE 90 tube directly connected with P 23AA gauge The volume pulse is obtained by recording electrical impedance changes between the tip of the catheter and a 21 gauge needle located subcutaneously right over the tip of the catheter The size of volume pulse has been adjusted so that its maximal height equals approximately that of the pressure pulse (original height 21 8 mm for P 20 8 mm for V) The ratio of areas of the two pulses 118 100 The arrow point at the difference in onset of the two pulses *Lower section* As above but the volume pulse is obtained from two subcutaneously inserted needles on each side of the femoral artery the pressure pulse is recorded from a 40 cm PE 90 tube advanced 9 5 cm up into the femoral artery until the feet of the two pulses coincide The height of the two pulses are exactly equal (original heights 17 0 mm for both) The ratio of the two pulse areas is 125 100 The pressure pulse contour is slightly damped because of the length of the catheter The beat to beat variability of the volume pulses is obvious in both records Calibration at the right is 0 1 ohm for impedance (vol me) and 0 50 100 150 mm Hg for pressure time in 0 1 second lines

*Mean and standard deviation.

relatively larger than the pressure rebound dicrotic wave. Therefore the subtraction curve becomes again negative and slopes off to zero only at the end diastolic period (Figs. 2 and 3). This is important because the time constant of the volume amplifier will tend to reduce the height of the volume pulse relatively faster than does the pressure (DC) amplifier. Fluctuations in the beat to beat configuration of the systolic portion of the volume pulse are frequent; diastolic portions of the volume pulse display variability related chiefly to respiration.

The over-all area of the volume pulse over its diastolic level exceeds in consequence the comparable area of the pressure pulse when the maximal deflections are made exactly equal. The mean ratio of these two areas in several resting pulses from the 13 cases was 127.30 ± 14.97 : 100.00 (volume : pressure); the coefficient of variation was 11.76 per cent.

3. Impedance pulses obtained with skin and subcutaneous electrodes. The arrival times of the volume pulses obtained with the two techniques did not differ, but pulses obtained with the subcutaneous electrode tended to display small elevations of higher frequency, mainly in late diastole; these occasionally obscured the exact onset of the upstroke. Respiratory waves and base line irregularities were more prominent with the subcutaneous electrode; furthermore, pulses obtained with this electrode were usually smaller so that higher gain had to be used in adjustment of their height. Another less obvious difference was the slower run-off time of pulses with the skin electrode; this is evident in Fig. 2 by the longer duration of the second negative phase of the subtraction curve. Despite these minor qualitative differences, the areas of several volume pulses obtained with the two methods in 4 persons studied more closely did not differ once their heights were equaled.

4. Effects of vasoconstriction and vasodilatation. None of these young subjects was a hyperreactor to the cold pressor or the breath-holding test. The delay in onset of the pressure decreased and on occasion the rise in the pressure pulse preceded the rise in the volume pulse. Also the pressure upstroke was usually accelerated so that the net mean time at which the subtraction curve returned to the base line (return time) in 7 persons studied more closely decreased from 0.039 ± 0.018 second to 0.011 ± 0.007 second during hypertension. These differences were not statistically significant, however, when



Fig. 2. Volume pulses (V) and pressure pulses (P) from the left brachial artery and instantaneous difference between the two (Δ) with electrocardiographic Lead II. The pressure pulse was recorded with a Cournand needle connected through a 30-cm. PE 280 catheter to a P23 VA gauge. The volume pulse represents impedance changes between the Cournand needle and a subcutaneous needle over its tip (*on the left*) and between the Cournand needle and a small lead electrode placed on the skin in the same location (*pulse on right*). The heights of the volume pulses have been adjusted to equal exactly those of the pressure pulses. The ratio of the areas of the two pulses on the left is 152 : 100; that of the pulses on the right is 155 : 100. Calibration and time lines as in Fig. 1.

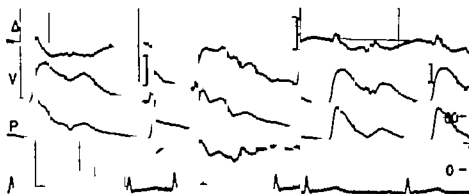


Fig 3 As in Fig 2 The volume pulses are obtained between the Cournand needle and small lead electrode on the surface over the tip of the needle Pulses on the left are recorded under control resting conditions the center pulses are recorded at the end of a 60 second period of breath holding and the pulses on the right are obtained few seconds after inhalation of amyl nitrite Calibration and time as in Figs 1 and 2 Observe the different gain of the amplifier for the impedance pulses in three section

paired comparisons were made on account of an increase in return time in one case The product moment coefficient of correlation between the return times before and during hypertension was −0 58 indicating a weak negative correlation between these two measurements in the same individual

Further qualitative changes in contour included a prolongation of the pressure systolic plateau and slower diastolic drop The volume pulses changed in many respects their size decreased so that to obtain a deflection equal in height to that of the pressure pulse the gain had to be adjusted up by varying degrees Furthermore evidence of viscous properties of the wall or of delayed compliance of change in volume with respect to change in pressure appeared Thus anacrotic breaks appeared leading to a late systolic peak of the volume pulse the delay of the dicrotic notch (volume) became longer In contrasting addition the diastolic sloping off toward the base line became faster so that the subtraction curve approached the base line or became positive in late diastole (pressure fall off was slower than volume fall off starting from identical systolic heights) As a result of this the ratio of the volume to pressure pulse areas decreased in 6 out of 7 cases the mean ratio decreased from 124 14 to 117 57 per cent The mean of these differences is −6 57 and its standard deviation is ±13 22 This decrease is not significant because of an increase in ratio in one of these 7 cases

Inhalation of amyl nitrite produced an accentuation of the normal volume pressure relations the volume pulse increased markedly in size and preceded the pressure pulse just as under the control conditions the peak of the volume pulse was reached early but during the rest of the cycle its size relative to the pressure pulse remained constantly larger

Discussion

Introduction of high frequency currents into tissues as a means of measuring segmental blood flow is a widely used method today [4] This method is based on the principle that at intermediate radio frequencies of the delivered current (around 100 1 000 kilocycles) most tissues are not stimulated the interelectrode segment behaves like a pure resistance and its reactive impedance factors approach zero Thus passive increase of the volume of the interelectrode segment will be directly related to the conductance between the electrodes and conductance changes can thus be used as an indicator of local changes in volume Choice of a somewhat lower oscillator frequency in the present unit (originally designed by Dr Otto Schmitt Minneapolis) was adopted for better penetration of interelectrode deep tissues whereas higher frequency currents would tend to flow on the skin surface

The described differences between pressure and impedance pulses of the examined arteries cannot be ascribed to phase lag of either one of the recording systems Most of the described differences are of low basal frequency and occur in the relatively stable parts of each cycle Relative lag or advance of features within both pulses frequently follow each other in the same cycle On the other hand the nature of the pulses is different the arterial pressure pulse is a physical difference of pressures in a closed system whereas the impedance pulse is a combination of arterial capillary and venous volume pulses between the two electrodes By keeping the interelectrode distance at a minimum one may reasonably assume that capillary and venous volume pulses are greatly reduced whereas the arterial capacity changes are unaffected Selective recording of changes in arterial volume can be assumed to have been obtained in the cases in which one electrode is the intra arterial tip of a polyethylene catheter and the other is the conducting tip of a short insulated needle positioned just outside the arterial wall at the level of the tip of the catheter The upstrokes of all recorded impedance pulses must be due solely to changes in arterial capacity which precede all capillary etc changes In fact if one uses two similar subcutaneous electrodes on either side of the artery the recorded volume pulse is not different from that obtained between a subcutaneous and an intra arterial electrode

The differences between volume pulses obtained with the skin electrode and those obtained with the subcutaneous one (against the same intra arterial electrode) must be ascribed to the large capillary volume of the interposed segment of skin this would account for the larger over all size smoother contour and slower diastolic decrease in pulses obtained with the skin electrode Changes in contact resistance between skin and electrode due to movement and reflected as impedance changes occur more easily with the subcutaneous electrode

The use of a scalar system (subtraction) to record such vectorial relations as bi directional relative changes of pressure and volume in time was imposed by reason of necessity we are aware of the shortcomings of this approach in expressing spatial relations The main advantage of this method is that the finer details of pressure volume relation have been made available to exact study in beat after beat and this could not be done by observing the vectorial loop on a cathode ray screen

Our results agree in part with those obtained by Rushmer who used a rubber mercury transducer to record changes in diameter of the aortic arch of dogs Circumference increased earlier but also faster than did the pressure in this area in his interpretation Rushmer invokes the proximity of the left ventricle which may pull as well as fill up the initial aortic segment such longitudinal effects should be only secondary in the experiments reported herein The faster increase of pressure (after a delayed start) in the present cases is probably due to the location studied In fact peripheral arterial pressure pulses have a significantly shorter build up time i e they rise faster than do central pulses [11]

In a recent extensive article Peterson and associates[4] have demonstrated by elegant and elaborate methods involving computer analyses a relative excess of volume over pressure pulse amplitude in canine arteries in situ during the major part of the downstroke This is in accord with the present findings and the authors attribute it to the viscous properties of the vessel wall locally applied epinephrine accentuates this delayed volume response during diastole (decreasing vascular stress cp also herein Fig 3 center) The two major differences between these data and ours are that (a) the upstroke differences reported herein are not obvious or referred to and (b) the canine volume pulse contours lack the higher frequency oscillations described here These differences may be due either to species differences or to the various differences in recording methodology employed As a consequence spectral analysis of Peterson data indicates that amplitude of harmonics of any volume pulse drops to the background noise level beyond the fourth harmonic of the basic frequency The data presented herein indicate the presence ...ble higher frequency com

the human volume pulse not present in the pressure pulse and probably extending into the eighth harmonic of the basic frequency (Fig. 1, lower half; Fig. 3).

If the artery were a completely rigid tube, no change in volume would be recorded with each cycle but only change in pressure. Actually, during each cycle the initial rise is that of volume,* but very rapidly (at about one tenth of the height of the volume pulse) the pressure also starts rising and overtakes the volume before its crest. The physical meaning of these relations cannot be determined with the present data, but it is interesting to note that during hypertension, in addition to decreased expansion and accentuation of the delayed compliance of volume to pressure during the plateau and early diastole, there is a *faster* return to the base line of the volume pulse during late diastole (Fig. 3, center). This suggests that under the conditions of the present experiments the relationship of pressure and volume may not be linear and that within *each cycle* periods of increased inertia (viscosity) and decreased inertia of the arterial wall may follow each other.

It should finally be noted that beat-to-beat variability of the volume pulses is marked in contrast to that of the pressure pulse. This variability is greatly reduced whenever segments of skin are involved between the electrodes and is more marked with subcutaneous electrodes. If, as discussed, such variability of volume pulse reflects changing uptake capacity of arteries, determination of cardiac output by the pulse contour method will be subject to errors related to this varying capacity. Such a possibility is more likely in peripheral muscular arteries.

In conclusion, the described pressure-volume relations of the brachial and femoral arteries of the young male are consistent with their nature as visco-elastic tubes. During short periods of hypertension these arteries become stiffer, inertial properties are exaggerated, and nonlinear elastic properties seem to appear; during amyl nitrite hypotension normal relations are accentuated. These changes indicate active participation of elements within the arterial wall in usual vasomotor reactions in addition to the changes of the terminal vascular bed.

*During extrasystoles occurring after [illegible] short diastoles, negative volume pulses have been recorded, unaccompanied by pressure pulses.

Summary

1. Pressure pulses and volume pulses were obtained simultaneously and from the same site of the brachial or femoral artery in 13 young men. Pressure pulses were obtained through a Cournand needle or a short PE 90 catheter connected to a Statham P23AA gauge and DC amplifier. Volume pulses were obtained by recording impedance changes between the Cournand needle or the tip of the catheter and a cutaneous lead disc placed over the tip of or a subcutaneous needle (insulated except its tip) inserted as near as possible to the tip of the Cournand needle or the catheter. The intra-arterial and extra-arterial needles were used for both introducing current and recording resistivity changes.

2. Recorded pressure and volume pulses were compared by adjusting the size of the latter to equal exactly that of the former. Pressure pulses were then fed as positive and volume pulses as negative input to a subtracting DC amplifier. The subtraction curve as well as the original pulses were simultaneously recorded.

3. The foot of the volume pulse preceded that of the pressure pulse by a mean of 0.010 second at the elbow. Thereafter, the rise in volume exceeded only briefly the rise in pressure. Thus, the peak was reached first for the pressure and then for the volume pulse. The mean time at which equal heights of upstroke were reached was 0.035 second. The dicrotic notch occurred later in the volume pulse, so that the over-all duration of volume systole exceeded by 0.04 to 0.06 second that of the pressure systole.

4. In diastole the height of the volume pulse decreased more slowly than did that of the pressure pulse. The over-all area of the volume pulse exceeded the comparable area of the pressure pulse despite equal maximal heights; the mean ratio of these areas in the 13 young men was 127:100. No major differences were observed between volume pulses recorded with a skin electrode and those recorded with a sub-

cutaneous electrode apart from stabler pulses obtained with the former electrode

5 Momentary hypertension was associated with volume pulses diminished in size their systolic phase lasted still longer but in diastole the return to the base line was faster The delay in onset of the pressure pulse got shorter and on occasion the rise in pressure preceded the rise in volume amyl nitrite reversed these trend

6 These data indicate that the brachial artery in the young is a partly distensible elastic tube whose wall becomes as a whole more rigid and inert during hypertension and more distensible during amyl nitrite hypotension Nonlinear relations of pressure and volume in parts of the cycle particularly in hypertension are suggested Beat to beat arterial capacity seems variable and thus justifies skepticism in regard to determinations of cardiac output with the pressure pulse contour method

7 Intravascular impedance plethysmography in association with simultaneous manometric data can give significant information on the properties of the vessel under study

REFERENCES

1 Frank O Die Grundform des arteriellen Pulses Ztschr f Biol 37 483 1899

2 Sahli H Die Sphygmobolometrie oder dynamische Pulsuntersuchung Abderhalden Handbuch der biol Arbeitsmethoden 5 1 75 1927

3 Donta A S Comparison of simultaneously recorded intra arterial and extra arterial pressure pulses in man Am Heart J 59 576 1960

4 Rushmer R F Pressure-circumference relations in the aorta Am J Physiol 183 545 1955

5 Peterson L H Jensen R E and Parnell J Mechanical properties of arteries in vivo Circulation Res 8 622 1960

6 Nyboer J Electrical impedance plethysmography Springfield Ill 1959 C C Thomas Publisher

7 Heyman F Comparison of intra arterially and extra arterially recorded pulse waves in man and dog Acta med scandinav 157 503 1957

8 Wiggers C J The pressure pulses in the cardiovascular system New York 1928 Longmans Green & Co

9 Hamilton W F The patterns of the arterial pressure pulse Am J Physiol 141 235 1944

10 Kroeker E J and Wood E H Comparison of simultaneously recorded central and peripheral arterial pressure pulses during rest exercise and tilted position in man Circulation Res 3 6 3 1955

11 Bonjer F H Van den Berg J and Dirken M N J The origin of the variations of the body impedance occurring during the cardiac cycle Circulation 6 415 1952

The application of boundary potentials to several electrocardiographic problems

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It is the purpose of this communication to briefly outline a particularization of the Gabor-Nelson equations[1] for the circular lamina with the purpose of determining the minimal number of electrodes which may be required to yield accurate dipole location.

In addition, a *short method* will be described by which dipole location may be determined accurately from the measurement of four boundary potentials.

In previous communications[2,3] it has been pointed out that the Wagner Ground reference potential of Frank and Kay is not, as they contend, equivalent to their arbitrary choice of zero potential at infinity. In these communications[2] it was stated that the Wagner Ground potential is in fact a function of dipole position and of dipole axis direction. It is the purpose of this communication to describe the Wagner Ground potential in mathematical terms with reference to the circular homogeneous lamina. In a previous communication[4] the Bayley[?] central terminal was described for use as a reference potential equivalent to that of zero potential at infinity. It is the purpose of this communication to support this argument with further expansions of dipole potential theory, with multipole potential theory, and with experimentations in which the net pole strength of the multipole is zero.

Method 1

The Gabor-Nelson equations for finding the dipole moment from a summation of the potentials on the boundary are[5]

$$(1)\quad \begin{cases} M_x = \dfrac{Rd}{\rho} \oint V \cos \theta\, d\theta \\ M_y = \dfrac{Rd}{\rho} \oint V \sin \theta\, d\theta \end{cases}$$

when particularized for the circular lamina. Here M_x is the moment of the dipole parallel to the axis of X; M_y is the moment of the dipole parallel to the axis of Y; R ($= 24.9$ cm.) is the radius of the circular lamina; d ($= 1.94$ cm.) is the depth of the conducting fluid measured in centimeters; ρ is the specific resistance of the fluid in ohm centimeters; V is the unipolar or bipolar potential at any boundary electrode or between one and all the other electrodes on the boundary; and finally θ is the angle made by the positive axis of X and the radius vector to the boundary electrode at which V is measured.

In our experience the most suitable way to determine the value of ρ is to measure the boundary potential V for the centric dipole where $\theta = 0$, that is, on the positive axis of X. Here $V = 2M/R$, and in the current experiments $V = 30$ mv. (Fig. 1). Now M is known to be equal to 373.5 Ma. cm. (Fig. 1). We also have $M = ID\rho/2\pi d$.[7]

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$$(2)\qquad V = \frac{2M\tau}{R}\left\{\frac{\lambda - f\lambda}{1+f^2-2f\gamma}\right\} + \frac{2M\tau_1}{R}\left\{\frac{\mu - f\mu}{1+f^2-2f\gamma}\right\}$$

$$(3)\qquad \begin{cases} \bar{Y}M - \bar{X}M = \dfrac{R^2 d}{\rho}\int V \cos(2\Phi)\,d\Phi \\ \bar{Y}M + \bar{X}M = \dfrac{R^2 d}{\rho}\int V \sin(2\Phi)\,d\Phi \end{cases}$$

$$(4)\qquad \begin{cases} V_x = \dfrac{2M}{R}\left\{\dfrac{\lambda - f\lambda}{1+f^2-2f\gamma}\right\} = \dfrac{2M(x-h)}{(x-h)^2+(y-k)^2} \\ V_y = \dfrac{2M}{R}\left\{\dfrac{\mu - f\mu}{1+f^2-2f\gamma}\right\} = \dfrac{2M(y-k)}{(x-h)^2+(y-k)^2} \end{cases}$$

If D (= 2.5 cm.) is the distance between the poles of the dipole electrode and I (= 5.3002 Ma.) (P.P.) is the current through the dipole electrode (determined by experimental measurement), we get ρ = 336 ohm cm for the specific resistance of tap water at the Oklahoma Medical Center. With these results it is clear that Rd/ρ = 0.1406 for the constant in Equation 1. There are two ways to obtain the value of V at any given number of points on the boundary of the circular lamina. They can be computed from the Equation 2 (*top of page*) or the value of V can be measured with reference to the potential V_T (=0) of an averaging network. In the following experiments V was computed by Equation 2 through four significant digits. The arbitrary dipole midpoint was chosen 3 cm along the positive axis of X and 1.0 cm along the negative axis of Y. The dipole axis was taken at 45 degrees from the positive X axis (Fig. 1). This rather laborious computation was done in order to remove errors which are introduced by the model or in reading the detector circuit. In Equation 2 τ is the cosine of the angle made by the dipole axis and the positive axis of X; τ_1 is the cosine of the angle made by the dipole axis and the positive axis of Y. λ and μ are the direction cosines of the angle between the X and Y axes and the radius vector R from O, the center of the circular lamina, to the point on the boundary at which V is measured. λ and μ are the direction cosines of the angles between the positive X and Y axes respectively and radius vector from O to the dipole midpoint, and finally γ is the cosine of the angle θ between the radius vector to any boundary electrode of potential V and the radius vector from O to the dipole midpoint (Fig. 1). Here $\gamma = \lambda\lambda + \mu\mu$. Also in Equation 1 $d\Phi$ is the increment of arc along the circumference of the circular boundary, and if V is taken at every 5 degrees of arc $d\Phi = 5\pi/180° = 0.0873$. If V is taken at every 10 degrees of arc $d\Phi = 10\pi/180° = 0.1745$, etc.

Table I shows that using 9 or more but not fewer electrodes gives satisfactory values of the first order moments M and M of the potential.

The Gabor-Nelson equations for the *second* order moments $\bar{X}$, $\bar{Y}$ of the boundary potentials as particularized for the circular lamina are as in Equation 3 (*top of page*) wherein $\bar{X}$ and $\bar{Y}$ are the coordinates in centimeters of the dipole midpoint position. All remaining symbols have been defined under Equation 1 and in the footnote to Table IIB. Examination of the two right hand columns in Table I shows that 9 or more but not fewer boundary electrodes at equal arc lengths are sufficient for accurate dipole midpoint location.

Method 2

If we denote by V the boundary potential when the dipole axis is parallel to the X axis and by V the boundary

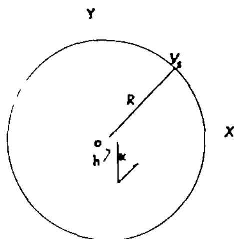


Fig. 1. Circular lamina of radius R with dipole midpoint location at the origin of the vector moment M at (h, k) from the center O. V is any boundary potential. The vector $\vec{R}$ from 0 to the origin of M not shown. The magnitude $R = \sqrt{h^2 + k^2}$. In the computations h = 3 and k = −10 (Table I). For this particular dipole location the Wagner Ground reference of Frank and Kay introduces a 44 per cent error in the origin of the rectangular coordinates on the image map. The *polar potentials* and the potential differences between the boundary electrodes and the Wagner Ground (V − V) all lie on the image circle of radius R = 36.40 mv. (P.P.). Here R = 2M/R(1 f²) (P. M. Berry.)

ntial when the dipole axis is parallel to the X axis. Equation 2 takes on the form of Equation 4 (*top of page 685*). We now have

(5) $X = V \quad V = (y - k)/(x - h)$

For the particular boundary electrode on the positive axis of X, $x_1 = 0$ and $x = R$. Equation 5 now gives $X = k$ (h R). For the particular boundary electrode on the negative axis of Y, $x = 0$ and $x = -R$. Equation 5 now gives $X = (R + k)/h$. We then have

(6) $k = \frac{R(1 - X)}{X - X} \quad k = \frac{RX(1 - X)}{X - X}$

where h and k are respectively the $\overline{X}$ and $\overline{Y}$ coordinates of the dipole midpoint. This result is obvious by inspection of Equation 5 where $R (= \sqrt{x^2 + y^2})$ is the radius of the circular lamina the center of which is located at (h, k) from the dipole midpoint position. By means of a precision mechanical stage for locating and relocating the dipole electrode (Fig. 2) and the detector circuit described elsewhere values of h and k may be determined to within 0.15 per cent accuracy. When h and k are solved these values may replace their identities in the right hand side of Equation 4 for a solution of the dipole moment M (Equation 2).

Method 3

It has been reported by this laboratory that V_w, the potential of the Wagner Ground, is a function of both dipole location and dipole axis direction.[4] Insofar as the circular lamina is concerned repeated experiments confirm this contention and show in fact that

(7) $V = \frac{\pi Rd}{\rho}\left(\frac{V + V}{2}\right)\cos\alpha$

or if the formulae for V and V are replaced in Equation 7 by their identities from Equation 2 the result is

(8) $V = \frac{ID}{2}\left(\frac{2f}{1 - f^2}\right)\cos\alpha$

In Equation 7 V and V are the two measured boundary potentials at the poles of a diameter of the circular lamina taken through the radius vector $\vec{R}$ drawn from the center of the circular lamina to the dipole midpoint with the dipole axis along the diameter specified. In using Equation 7 V and V are measured directly in millivolts (P.P.). Also α is the angle made by the positive axis of the dipole and $\vec{R}$. R is the radius in centimeters of the circular lamina, d is the depth in centimeters of the fluid conductor (tap water) and ρ is the specific resistivity in ohm centimeters of the conducting fluid. In Equation 8 I is the R.M.S. current through the dipole electrode and D is the distance in centimeters between the outer surfaces of the dipole electrode. If ID is determined in R.M.S. value then ID/2 in Equation 8 holds. For comparable values determined by Equation 7 where V and V were measured in peak to peak values ID/2 is multiplied by $2\sqrt{2}$ and the constant in Equation 8 becomes $ID\sqrt{2}$. The central terminal of potential V_T from 72 boundary electrodes has been shown to have a zero of potential equivalent to zero potential

at infinity[1,2,3] and moreover V_T is independent of dipole location or dipole axis direction. We can thus measure V_w, the Wagner Ground potential directly using the lead

$$(9) \qquad (V - V_T) = V$$

Consequently, Equations 7, 8, and 9 offer three methods for a determination of V_w. Table IIA gives the results of all three methods using 17 values for fR, the magnitude of the dipole eccentricity. During these experiments the dipole axis was arbitrarily kept in the direction of the positive X axis which in turn was chosen along the line of eccentric positions. Consequently, when the eccentricity was along the positive X axis, cos α (= +1) gave positive values for V, but when equal eccentricities were taken along the negative X axis, cos α (= −1) gave negative values for V_w (Table IIA). Moreover, rotations of the dipole axis at all eccentricities precisely described the proportional function cos α of Equations 7 and 8.

Method 4

The Nelson formula[9] for the potentials on the boundary of an ellipse was programmed on the 650 IBM computer for boundary potentials at equal central angles of every 5 degrees.[3] This program was changed to compute the potentials at 72 *equal lengths of arc* around the boundary of the ellipse. Three ellipses of markedly different shape were used, together with two different dipole positions in each ellipse. In all six instances the sum of the 72 bound

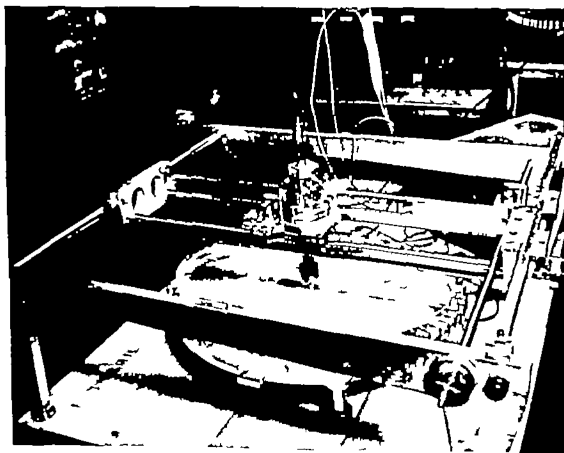


Fig. 2. Precision mechanical stage with four dimensions of freedom: motion along X, along Y, and along Z. The electrode stage proper permits accurate degrees of rotation of dipole axis. Positioning of the dipole midpoint is accurate to within 0.002 cm. Dipole electrode is depicted at the center of the elliptical lamina. All resistors (2) are equal with tolerance of 1 per cent and may be seen connecting the boundary electrodes to the averaging buss of potential V. The electrodes are spaced at equal lengths along the boundary of the ellipse.

Table I Dipole moments and dipole midpoint coordinates computed with the Gabor Nelson formulae for the circular lamina

	Equation 1		Equation 3	
	M (P P)	M (P P)	$\overline{X}$ (cm)	$\overline{Y}$ (cm)
72	9 378	9 379	3 00	−10 00
36	9 369	9 371	2 99	−10 00
24	9 397	9 406	3 02	−10 03
18	9 366	9 373	2 99	−9 99
12	9 371	9 367	2 99	−10 00
9	9 358	9 403	3 08	−9 99
9	——	——	2 98	−9 99
Correct loc	9 366	9 366	3 00	−10 00

the number of bou d y el ct des Under M and M are th dipol moments computed from Equatio 1 and 2 Under $\overline{X}$ d $\overline{Y}$ are the coo d te espect vely of the dipole midpoint position Th y given in centim and were computed using Equation 3 Th ese values d p ndent of the l use l in comp g M and M but depe d upon the ratio M /M When is 6 abou f M d M re unsatisfacto

ary potentials was zero This result indicates that if V is the potential defined by the Nelson equation[1] we must have

$$(10) \qquad \overline{V} = \oint V \, ds = 0$$

for any dipole location in an ellipse of any shape In Equation 10 $\overline{V}$ is the average value of the boundary potentials V and ds is an element of arc If ds is an element of surface and $\oint$ indicates a surface integral *Equation 10 holds for any body of nonre entry form*

To confirm Equation 10 experimentally 72 electrodes spaced at equal arc lengths along the boundary of the ellipse a/b = 1 32 were connected to a central terminal through *equal* resistances (Fig 2) The potentials (V − Vr) were then measured using an arbitrary dipole position and these potentials were compared with the unipolar potentials computed by the 650 IBM computer programmed on the C V Nelson formula The experimental results were highly satisfactory Thus Equation 10 is confirmed by both computer and laboratory experimentation

Equations of the types 1 and 3 were particularized for dipole location in the ellipse of arbitrary shape and programmed for the 650 IBM computer Table III shows the computed dipole locations which resulted from two sets of potential measurements using the generator and detector circuit described elsewhere[3] These potentials are comparable in accuracy to those which can be measured with modern photographic electrocardiographic equipment

Discussion

The Gabor Nelson equations[1] when particularized for the circular and the elliptical lamina result in accurate dipole midpoint location when more but not fewer than 9 *boundary potentials or potential differences* enter these summations Inasmuch as these equations are completely general for a nonre entry form of three and two dimensional shapes when locating a dipole (or a multipole of higher order) by the arbitrary measurement of boundary potentials or potential differences these equations must be regarded as the most *important* mathematical contribution to electrocardiography since that of Helmholtz[11] in 1853

The short method of dipole midpoint location in the circular lamina is equally accurate when used with a precision mechanical stage for the dipole electrode (Fig 2) These simple equations (4 5) may be equally useful when using a turtle heart beating in a circular lamina or in studying an arbitrary multipole (of zero net pole strength) located centrically or eccentrically in the circular lamina

When unipolar potentials are used with a beating heart it will be necessary to in

Table IIA The values of the Wagner Ground potential V as determined by Equations 7, 8 and 9 for various values of eccentricity fR

fR (cm)	Equation 7 V (mv)	Equation 8 V (mv)	Equation 9 V (mv)	Sphere factor
0	0	0	0	
±2 54	±1 32	±1 36	±1 50	2 52
±5 08	±2 87	±2 82	±2 95	2 59
± 67	±4 56	±4 47	±4 50	2 [illegible]
±10 16	±6 51	±6 48	±6 25	2 90
±12 70	±9 27	9 12	±9 00	3 70
±15 24	±12 81	±12 96	±13 00	3 70
±17 78	±19 1	±19 30	±19 20	4 58
±20 37	±31 80	±37 36	±33 50	6 49

The [illegible] I = 1.0742 Ma (R M B) D = 2 1 ID 2 = 6 6233 d = 1 94 cm R 24 9 cm = [illegible] and R/d = 0 4417 The measured values of (V + V)/2 are shown in Table IIB along with the computed values of 2f/(1 − f²) According to Equation 7 the values of (V + V) [illegible] multiplied by 0 4417 and the values f/(1 − f²) of Equation 8 [illegible] multiplied by 6 6233 All values for V are given [illegible] peak-to-peak At each value of the eccentricity the dipole was rotated through 60 [illegible] the [illegible] In the first instance the [illegible] of V [illegible] to [illegible] half of the [illegible] been under V of Equation 9 [illegible] V [illegible] These and other degrees of rotation at all 6 values of [illegible] that V was proportional to [illegible] as described in Equations 7 and 8 Column five under sphere [illegible] the number of [illegible] the Wagner Ground [illegible] V would be [illegible] where [illegible] the spherical [illegible] For example fR = 12 0 cm [illegible] the [illegible] V at 9 12 [illegible] the circular [illegible] In the spherical conductor the value [illegible] by 3 70 times

troduce four simultaneous potentials in order to eliminate the unknowns Φ and Ψ in a solution of h and k. Similar transformations apply to a three-dimensional homogeneous media.

Under Method 3 are described three different approaches to a solution of the Wagner Ground reference potential of Frank and Kay. The three methods yield essentially identical results and may be regarded as a conclusive demonstration of the nonunipolar Wagner Ground error. The absolute magnitude of this error is not widely appreciated. In the current study the average magnitude of 72 values for V (without regard to sign) was 20 23 mv (P P) with a maximum of −43 90 mv (P P) on electrode Φ = 255 and a minimum of −0 41 mv (P P) on electrode Φ = 145. Consequently Table IIA indicates that for all values of fR other than zero the Wagner Ground error is such as to make this reference unacceptable for the direct measurement of *unipolar* potentials.

It has been suggested by Gaselowitz[14] that the Wagner Ground error of Equation 9 would be minimized by having the poles of the dipole electrode smaller and separated by a smaller distance D of Equation 8. The results on V in column three of Table IIA are computed by the dipole Equation 8 where the separation of point poles is infinitesimal and their agreement with the data of columns two and four does not appear to support these contentions. Gaselowitz has also reported[14] that the Wagner Ground error might be minimized in using a three rather than a two dimensional conductor. Examination of column five of Table IIA together with column three of Table IIB shows that the Wagner Ground error V is increased rather than decreased in passing from a circular disk to a sphere. One has only to multiply the potentials in column three of Table IIA by the numbers in column five of that table.

Table IIB Measured and computed values for determining V by Equations 7 and 8 respectively

fR (cm)	(V + V)/2 (mv)	2f/(1 − f²) (circle)	2 − f²/(1 − f²) (sphere)
0	0	0	
±2 54	3 00	0 2061	2 521
±5 08	6 50	0 4	58
±7 62	10 30	0 6	2 70
±10 16	14 7	0 9789	2 899
±12 70	21 00	1 3 86	3 203
±15 24	29 00	1 9569	3 698
±17 8	43 50	2 9131	4 581
±20 3	2 00	4 8942	6 488

The values under (V + V)/2 were measured and the values under 2f/(1 − f²) were computed. The quantity [illegible] when multiplied by 2f/(1 − f²) gives (except for the [illegible]) 1/2 (V + V) for the [illegible] Here again V and [illegible] are defined as the boundary potentials [illegible] points [illegible] diameter taken through the radius vector fR drawn from the center of the sphere to the pole midpoint. The [illegible] of these potentials [illegible] the diameter [illegible] When [illegible] directed the function [illegible] takes care of both the sign and magnitude of V and [illegible] these results [illegible] be compared to the Wagner Ground. This includes [illegible] transforms which [illegible] the [illegible] the dipole [illegible]

Table III. Dipole midpoint coordinates computed by the 650 IBM computer using the Gabor-Nelson equations for the elliptic lamina

	X (cm.)	Y (cm.)
72	−4.96	−7.58
36	−4.88	−7.59
24	−4.96	−7.63
18	−4.91	−7.57
12	−5.02	−7.58
Correct values	−5.08	−7.62

The dipole potential differences between electrodes θ = 0° and all of the 72 electrodes located at equal [illegible] on the boundary of an elliptical lamina were measured for each of two dipole axis directions 90 degrees apart. These potentials [illegible] into the 650 IBM computer [illegible] calculation of the dipole midpoint coordinates. The [illegible] shown in the table. Note that the 24 potentials from 12 electrodes [illegible] lengths) [illegible] midpoint locations [illegible] as the 144 potentials from 72 electrodes. [illegible] measured with slightly better [illegible] than those which might be obtained from the [illegible] high-speed photo[illegible] electrocardiogram. Dipole [illegible] conducting lamina [illegible] (Computer work [illegible] by P. M. Berry [illegible] Computer Laboratory [illegible] Oklahoma [illegible])

to obtain the Wagner Ground unipolar error for the sphere.

Examination of Equations 7, 8, and 9 together with Tables IIA and IIB makes clear the nature and magnitude of the Wagner Ground error V_w. With reference to the *dipole generator network*, V_w is a *kind* of dipole midpoint potential. With reference to the zero of potential at infinity, V_w of Equation 9 *agrees* precisely with the zero of potential adopted in the *mathematical* theory of Frank and Kay.[4] If V_w is used according to the method proposed by Frank and Kay, the dipole *must be confined to the centric position* in the circular lamina or in the sphere where f = 0, or the medium must be made infinite. V_w can be used as a reference potential for unipolar potential measurements with eccentric dipole positions in plane or in volume conductors of finite extent when and only when its *explicit potential function is known*. The value of the potential function can then be subtracted from the potential difference measured for obtaining the unipolar value. The V_w function is changed when the boundary contour is changed, and we have not as yet solved this function for the ellipse. In transfer of the dipole electrode to the torso model from the sphere or hemisphere, Frank and Kay introduced an unknown potential function for V_w which vanished upon return to centric position of the simple model. In the simple conductors studied in this laboratory, V_w is shown to be a function of certain *boundary potentials* when compared to the arbitrary zero of potential at infinity or when compared with any potential that differs from this zero by at most a constant while the location of the dipole midpoint and the direction of the dipole axis are allowed to vary. V_w has the added disadvantage of being thermolabial and chemolabial across the contact surfaces of the dipole electrode.

Equation 10 appears to hold for a plane or volume conductor of any nonre-entrant shape, and V may be regarded as the potential at any boundary point due to any multipole of zero net pole strength. This generalization is supported further by the residue theorem for the complex variable.[5] Electrodes which are equally spaced on a broad elastic belt that stretches onto the chest at the heart level results in an electrode spacing at *equal arc lengths*. This system of electrodes[6] can then be connected to a common terminal through *equal resistances*. This terminal has then a potential equivalent to the customary choice of zero potential at infinity.[4,6] A belt of similar construction using 9 or more electrodes can be utilized for dipole location provided 18 or more potentials are entered into the summations of the Gabor-Nelson equations (Table I).

Summary

1. The Gabor-Nelson equations require a minimal of 18 or more boundary potentials or potential differences for computation of dipole midpoint location in the insulated two-dimensional conductor. The 18 or 24 potentials are best taken from 9 or 12 electrodes, respectively, using two dipole axis directions.

2. The Wagner Ground reference potential of Frank and Kay is shown to be a function of certain *boundary potentials*. This function *changes* when the *boundary*

contour is *changed* Its explicit formula is presented for the circular lamina and for the sphere

3 The equation for central terminal of zero potential using equal resistances is presented for an ellipse of any shape Its validity is supported by computer experiments and by laboratory investigation

4 Experimental and computer data indicate that highly accurate dipole location may be obtained in the circular or in the arbitrary elliptical lamina using 18 potentials from as few as 9 boundary electrodes

Thanks are due to Mr P M Berry for the computer program and t Grad Jeter for potential measurements on the ellipse

REFERENCES

1 Gabor D and Nelson C V Determination of the resultant dipole of the heart from measurements on the body surface J Appl Physics 25 413 1954
2 Bayley R H Unipolar potential measurements in the electric field produced by an arbitrary dipole in circular homogeneous lamina Circulation Res 7 537 1959
3 Bayley R H Measurements of unipolar potentials in the electrical field produced by an arbitrary dipole in the elliptical homogeneous lamina Am Heart J 59 737 1960
4 Frank E and Kay C F A reference potential for unipolar electrocardiographic measurements on models Am Heart J 46 195 1953
5 Bayley R H Exploratory lead systems and zero potentials Ann New York Acad Sc 65 1110 1957
6 Nelson C V Personal communication July 7 1960
7 Bayley R H The electric field produced by an eccentric dipole in homogeneous circular conducting lamina Circulation Res 272 1959
8 Wilson F N Macleod A G and Barker P S The distribution of the currents of action and of injury displayed by heart muscle and other excitable tissues Ann Arbor 1933 University of Michigan Press
9 Nelson C V and Gastonguay P A definition for zero potential Circulation Res 1039 1959
10 Nelson C V Human thorax potential Ann New York Acad Sc 65 1014 1957
11 Wilson F N and Bayley R H The electric field of an eccentric dipole in homogeneous spherical conducting medium Circulation 1 84 1950
12 Nelson C V Personal communication August 8 1960
13 Gaselowitz D Personal communication December 1959
14 Churchill R V Introduction to complex variables and applications New York 1948 McGraw Hill Book Co Inc

Case report

Paroxysmal ventricular tachycardia associated with myxedema A case report

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Ventricular tachycardia rarely occurs in the absence of serious heart disease especially in a patient over 40 years of age In the case reported the usual etiologies of paroxysmal ventricular tachycardia were not found and simultaneously occurring myxedema was believed to be the cause

Case report

A 42 year-old housewife was admitted to an army hospital on March 29 1959 because of ventricular tachycardia The patient had enjoyed excellent health until the summer of 1958 when fatigability and menometrorrhagia began Administration of ferrous sulfate resulted in a rise in her hemoglobin from 9 5 to 12 0 Gm

Uterine dilatation and curettage in December 1958 showed late secretory phase endometrium A chest x-ray film at this time showed in the right lower lung field a partially calcified density which had enlarged since examination a year before Intradermal coccidioidin and histoplasmin tests were positive the second strength tuberculin test was negative A large granuloma was removed from the right lower lobe on J 16 1959 No specific etiology was established by microscopic or cultural examination Convalescence was slow

After discharge from the hospital on Feb 4 1959 she became so exhausted that she could not return to her normal activities She noted increasing weakness lameness and puffiness of the hands and puffiness of the face especially about the eyes Although she was a talented musician she lost her ability to sing She was aware of thinning of the axillary and scalp hair but unaware of any mental retardation or definite cold intolerance

On March 27 1959 she developed a cough sore throat and coryza which cleared by the following evening After breakfast on March 29 she suddenly noted light headedness and darkening of the vision followed by an oppressive tight substernal discomfort and feeling of suffocation A few moments later she was aware of her heart pounding The chest discomfort was replaced by a burning sensation of the forearms The pounding ended abruptly less than 10 minutes after onset The patient estimated that 12 to 15 similar episodes occurred during the day each lasting from 3 to 10 minutes and accompanied by chest pain of less than 5 minutes duration The patient had never before experienced palpitation light headedness shortness of breath or arm or chest pain or pressure She did not smoke and had not been emotionally upset There was no family history of endocrine or heart disease Her mother an asthmatic died at age 49 Her father 11 siblings husband and three children were all in apparent good health

The patient was seen in the emergency room where an electrocardiogram showed multifocal premature ventricular contractions and abnormal T waves (*1830 March 29* Fig 1) While being observed there she suddenly felt faint The pulse was then found to be 190 and the blood pressure was 80/70 mm Hg Carotid massage eyeball pressure and tongue pulling had no effect The electrocardiogram at that time showed ventricular tachycardia (*2200 March 29* Fig 1) The tachycardia lasted approximately 30 minutes and stopped spontaneously while she was enroute to the ward

Further examination revealed a sallow-complexioned gray haired cooperative psychomotor retarded and apprehensive Caucasian female Her height was 67 inches weight 128 pounds temperature 98 6 F pulse 80 and blood pressure 90/72 mm Hg The scalp hair was sparse coarse and dry Facial edema was evident in retrospect The pharynx was slightly reddened but there was no exudate or adenopathy The thyroid was not palpable The heart tones were of poor quality \

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murmurs were heard There was no evidence of congestive failure Deep tendon reflexes were present but there was marked pseudomyotonia and weakness of the skeletal muscles There was no abnormal pigmentation in the surgical scars The palms of the hands and soles of the feet were conspicuously yellow

The chest ray film revealed scattered pulmonary calcifications The heart size and shape were normal The leukocyte count was 13 200 with 80 per cent neutrophils 15 per cent lymphocytes 4 per cent monocytes and 1 per cent eosinophils The hemoglobin was 13 5 Gm per cent hematocrit 37 per cent erythrocyte count 3 870 000 platelet count 220 000 sedimentation rate (Wintrobe) 40 mm uncorrected glutamic oxalacetic transaminase 22 units glutamic pyruvic transaminase 7 units protein bound iodine 1 9 micrograms per cent and serum cholesterol 309 mg per cent The heterophil antibody titer was

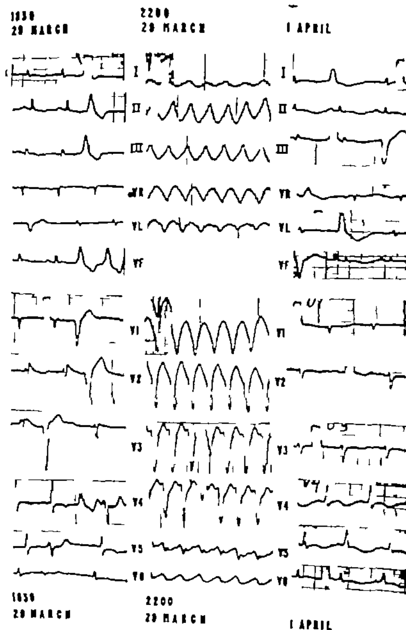


Fig 1 Electrocardiograms recorded on day of admission and 3 days later Frequent ventricular premature contractions are seen in left and right tracings Middle tracing shows ventricular tachycardia no definite P waves are seen Note similarity of premature ventricular contraction complexes in first tracing to those of the parox

1 112 differential absorption was not done. The basal metabolic rate was −32. The urinalysis, cardiolipin, serum protein, calcium and phosphorus and two throat cultures were normal.

The patient was maintained initially on small quantities of phenobarbital and 1.2 to 1.6 Gm. of quinidine sulfate daily. She had no further chest pain nor recognized episodes of tachycardia. She remained afebrile without evidence of congestive failure. Urine output was adequate. The blood pressure stabilized in the range of 97-72/70-60 mm. Hg. The heart tones remained poor. There were no murmurs but occasionally a dull or leathery third heart sound was heard. Serial electrocardiograms showed further lowering of the QRS amplitude, nonspecific T-wave abnormalities, prolongation of the Q-T interval, and premature ventricular contractions (Figs. 1 and 2). There was no evidence of myocardial infarction. Daily leukocyte counts and blood smears were normal. No atypical lymphocytes were seen.

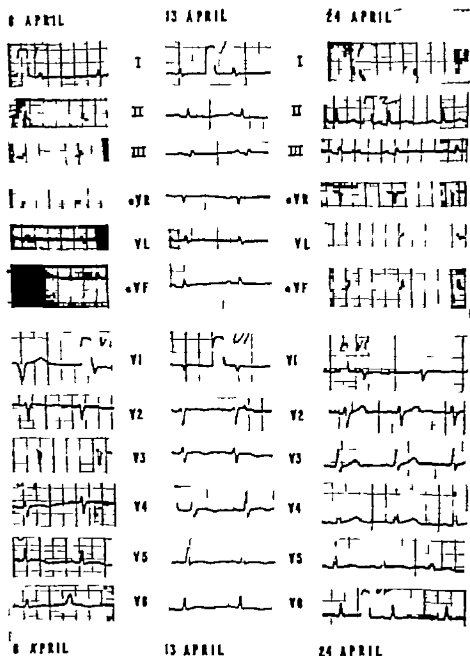


Fig. 2. Electrocardiograms recorded on day prior to institution of thyroid therapy and after 6 and 19 days of thyroid therapy. Note gradual but definite increase in voltage of QRS complexes, change from inverted to normal T waves, and cessation of ventricular premature contractions.

Serum transaminase (SGOT and SPT) determinations of March 30 and 31 and April 1, 2, 3 and 6 were normal. Chest x-ray films taken on April 6 with the patient in the upright and supine positions were unchanged.

Fifteen milligrams of thyroid extract daily was started on April 7. The daily dosage was gradually increased to 120 mg by April 17. Full ambulation was allowed by April 13. No premature ventricular contractions were noted on frequent electrocardiograms after April 13 except for two such contraction on April 22. The electrocardiogram showed marked improvement by April 24 (Fig. 2) and became normal May 1. The patient's blood pressure rose to the range of 108-100/80-0 mm. Hg. The basal metabolic rate rose to −9. The patient was discharged from the hospital April 24 feeling warmer, stronger and less clumsy. The protein bound iodine was 4.1 μg per cent and the serum cholesterol was 191 mg per cent on May 1, 1959. By late May 1959 the patient had lost 9 pounds and was strikingly improved in appearance, intellect, strength and coordination. Normal menses returned. She has been maintained on 120 mg. of thyroid extract daily. In December 1960 she felt well and had normal electrocardiogram, hemogram and blood chemistries.

Discussion

Although the patient's history is complicated by the removal of the granuloma of the right lower lobe of the lung, her hypothyroidism apparently began in mid 1958. Her symptomatology, laboratory data, and striking response to the administration of thyroid extract made the diagnosis of myxedema certain. An additional endocrinopathy, such as hypopituitarism, was most unlikely because of her lack of amenorrhea and her satisfactory response to thyroid alone.

Paroxysmal ventricular tachycardia is difficult to diagnose with certainty, even with the electrocardiogram. Despite the fact that separate P waves could not be identified during the paroxysm, the tracing of 2:00 March 9 (Fig. 1) is believed to show ventricular tachycardia for the following three reasons: (1) the tachycardia failed to respond to vagal stimulation; (2) all recorded premature contractions before and after the paroxysm were ventricular in origin (wide complexes with compensatory pause as in Leads II, aV_L, V, V and V on March 29); and (3) the R-R interval was not absolutely regular during the paroxysm (best seen here in Lead V).

The causes of paroxysmal ventricular tachycardia as given in standard texts and collected series are[1-8] (1) coronary atherosclerosis, especially after an acute myocardial infarction; (2) severe valvular heart disease, rheumatic or syphilitic; (3) severe hypertensive heart disease; (4) Wolff-Parkinson-White syndrome; (5) toxicity to digitalis or quinidine; (6) excitement, exercise, or emotional upset in an apparently normal individual; (7) thyrotoxicosis; (8) acute rheumatic fever; and (9) diphtheria or other acute infections. Individual case reports ascribe its occurrence to metastatic neoplasms, Hodgkin's disease, sarcoidosis, idiopathic pericarditis,[11] and the use of anesthetics[4] or antimony compounds.[14]

None of these causes was found, although the effect of myxedema on the brain, the presence of a mild respiratory infection, and a possible mild or moderate degree of coronary atherosclerosis may have been significant.

Sinus tachycardia, paroxysmal or chronic auricular fibrillation, and to a lesser extent other supraventricular tachycardias are very common in hyperthyroidism. However, only two cases with the combination of hyperthyroidism and ventricular tachycardia could be found in the literature. The first[17] was that of a 58 year-old Negro woman with a goiter, congestive failure, syphilis, a markedly enlarged heart, a basal metabolic rate of +38, and auricular fibrillation. In this patient a paroxysm of six successive complexes of ventricular origin was recorded. The second case[3] was that of a 44 year old woman with auricular fibrillation, cardiomegaly, congestive failure and goiter who was given large amounts of digitalis. As the ventricular rate decreased, premature ventricular contractions increased, culminating in runs of ventricular tachycardia. Both cases then were complicated by congestive failure and auricular fibrillation, one by syphilis and the other by digitalis intoxication. Several eminent cardiologists could not recall having seen the combination of hyperthyroidism and ventricular tachycardia.[18,19] One wonders whether hyperthyroidism alone is a cause of ventricular tachycardia.

Ullrick and Whitehorn[20] using the tissue slice technique with rat muscle demonstrated that under the influence of thyroid hormone the basic respiration of auricular muscle (that is, oxygen requirement) is

more markedly increased than is that of the ventricular or skeletal muscle. Myocardial hypoxia increases myocardial irritability and the tendency to arrhythmia.[24] This relative sensitivity of the auricular musculature to the action of thyroid hormone offers a physiologic basis for the propensity to auricular tachycardias so characteristic of hyperthyroid heart disease. As far as is known, the converse experiments have not been made, i.e., the change in auricular and ventricular muscle respiration in hypothyroidism has not been noted.

The induction of the hypothyroid state with radioiodine has been found to reduce noticeably the incidence of supraventricular tachycardias in previously euthyroid individuals with rheumatic and arteriosclerotic heart disease.

Sinus bradycardia and first degree heart block are common in hypothyroidism and improve with the administration of thyroid extract. Other rhythm abnormalities, that is, paroxysmal auricular fibrillation, flutter, and tachycardia, and nodal tachycardia have been reported in patients with myxedema. In these patients the abnormal supraventricular rhythms have on occasion reverted to normal after the administration of thyroid extract.[7,10] The inconstancy of this conversion and the presence of coexistent heart disease make it difficult to draw a cause and effect relationship.

Ventricular tachycardia has not, to my knowledge, ever been attributed to hypothyroidism, either spontaneous or induced. If ventricular tachycardia did occur in a patient with heart disease and induced hypothyroidism, it would probably be attributed to the underlying heart disease. As an example, Graybiel, White, Wheeler, and Williams[21] in their textbook of electrocardiography show the tracing of a 45-year-old man on thiouracil. The electrocardiogram had abnormal T waves and short runs of ventricular paroxysmal tachycardia. The basal metabolic rate of their patient was −25 at that time. He had been thyrotoxic 4½ months before, at which time his electrocardiogram was borderline. Coronary artery disease was postulated as a possible explanation for the high degree of cardiac irritability. It is possible that the patient's hypothyroid state was also significant.

What caused the ventricular tachycardia in our patient? For the following reasons myxedema is considered to be the primary cause of the myocardial dysfunction and resultant paroxysmal ventricular tachycardia. (1) A marked reduction in cardiac output and oxygen consumption is a consistent finding in myxedema.[1] Resultant myocardial hypoxia increases the tendency to arrhythmias. (2) The patient's premature ventricular contractions and abnormal electrocardiogram cleared promptly after the administration of thyroid extract and did not return. (3) No other cause of myocardial dysfunction or ventricular tachycardia could be found.

Although the causal relationship between hyperthyroidism and auricular tachycardias is firmly established, the relationship between hyperthyroidism and ventricular tachycardias is tenuous and may not exist.

Summary

A 42-year-old woman with myxedema and paroxysmal ventricular tachycardia is reported. Her electrocardiogram became normal and premature ventricular contractions ceased after the administration of thyroid extract. In the absence of other known causes for the ventricular tachycardia, it seems likely that myxedema was the initiating cause. The relationship of the thyroid gland to cardiac arrhythmias is briefly discussed.

REFERENCES

1. Katz, L. N., and Pick, A.: Clinical electrocardiography. Part I. The arrhythmias with an atlas of electrocardiograms, Philadelphia, 1956, Lea & Febiger.
2. Armbrust, C. A., and Levine, S. A.: Paroxysmal ventricular tachycardia: a study of one hundred and seven cases, Circulation 1:28, 1950.
3. Bellet, S.: Clinical disorders of the heart beat, Philadelphia, 1953, Lea & Febiger.
4. Friedberg, C. K.: Diseases of the heart, ed. 2, Philadelphia, 1956, W. B. Saunders Co.
5. Harrison, T. R., Resnik, W. H., and Hecht, H.: Diagnostic aspects of heart disease. *In* Harrison, T. R., Adams, R. D., Beeson, P. D., Resnik, W. H., Thorn, G. W., and Wintrobe, M. M.: Principles of internal medicine, ed. 2, New York, 1954, McGraw-Hill Book Co., Inc.
6. MacBryde, C. M.: Signs and symptoms, ed. 3, Philadelphia, 1957, J. P. Lippincott Co.
7. Stewart, H. J.: Cardiac arrhythmias. *In* Cecil, R. L., and Loeb, R. F.: A textbook of medicine, ed. 10, Philadelphia, 1959, W. B. Saunders Co.
8. Wood, P.: Diseases of the heart and circulation

ed 2 Philadelphia 1956 J P Lippincott Co

9 Yater W M Fundamentals of internal medicine ed 3 New York 1949 Appelton Crofts Century Inc

10 Halaur I and Halmos T Clinically diagnosed cardiac metastasis causing ventricular tachycardia Orvosi Hetilap 99 705 1958

11 Gerard G LaTour H Puech P and Olivier G Tachycardie paroxystique ventriculaire et pericardite par maladie de Hodgkin controle oesophagien d une crise tachycardique et de sa reduction Arch mal coeur 1 635 1958

12 Felkai B Ormos J and Rak K Ventriculare paroxysmale Tachykardie bei einem mit pulmonaler Embolie erbundenen Fall von myokardialen Sarkoidose Klinisch pathologische Studie Ztschr ges inn Med 13 355 1958

13 Morris G M and Franklin R B Ventricular tachycardia due to idiopathic pericarditis controlled by simultaneous intravenous procaine amide and quinidine AM HEART J 4 919 1954

14 Millar R A Gilbert R G and Brindle G F Ventricular tachycardia during halothane anaesthesia Anaesthesia London 13 164 1958

15 Schock R Patterband A B and Lieberman A H Fundus therapy of schistosomiasis associated with ventricular tachycardia and death case report Ann I t Med 46 39 1957

16 Blumgart H L Freedberg A S and Kurland G S Hypercholesterolemia myxedema and atherosclerosis Am J Med 14 665 1953

17 Wolferth C C and McMillan T M Paroxysmal ventricular tachycardia Arch Int Med 31 184 19 3

18 Luten D Clinical studies of digitalis advanced toxic rhythms Arch I t Med 35 87 1925

19 Andrus E C Personal communication

20 Bellet S Personal communication

1 Katz L N Personal communication

22 Pollock B E Personal communication

23 Ullrick W C and Whitehorn W V Influence of thyroid hormone on respiration of cardiac muscle Am J Physiol 171 407 1952

24 Harris A S Bisteni A Russell R A Brigham J C and Firestone J E Excitatory factors in ventricular tachycardia resulting from myocardial ischemia potassium a major excitant Science 119 200 1954

25 Blumgart H C Freedberg A S and Kurland G S Radioactive iodine treatment of angina pectoris and congestive heart failure Circulation 16 110 19 7

26 Corday E Gold H and Jaffe H L Radioiodine treatment of paroxysmal supraventricular tachycardia in the euthyroid patient Circulation 1 900 1955

27 Ohler W P and Abramson J The heart in myxedema Arch Int Med 53 165 1934

28 Barr D P The heart in diseases of the endocrine gland *I* Stroud W D and Stroud M W III Diagnosis and treatment of cardiovascular disease Vol I Philadelphia 1957 F A Davis Co

29 Lerner H and Anderson E M Three cases of adult myxedema in women Endocrinology 1 355 1931

30 Gant J C Myxedema heart report of a case New Eng and J Med 213 918 1935

31 Graybiel A White P D Wheeler L and Williams C Electrocardiography in practice ed 3 Philadelphia 19 4 W B Saunders Co

32 Ellis L B Mebane J G Swaiah G Hultgren H N and Bloomfield R A The effect of myxedema on the cardiovascular system AM HEART J 43:341 1952

Clinical pathologic conference

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James Kalokerinos M B D M R D
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Clinical abstract

The patient was 24-year-old married woman who had one son aged 2¼ years Her illne began in July 1959 ith symptoms ttributed to in fluenza namely hard unproductive cough dizziness feeling of heaviness in the head general ised aches and pains and retrosternal pain ex acerbated by coughing and deep respiration Such little expectoration as appeared was white but it was occasionally streaked ith blood Tubercle bacilli were looked for but not found The illness *did not soon abate like influenza but continued* eek after eek I August she first noticed breath lessness and palpitation t first onl on exertion but later even on light activity After October she coughed up no more blood for man eeks In December 19 9 an x ray film of her chest was made t a local ho pital and a reported to show patchy consolidation t the left lung base and minimal amount of fluid in the left pleural ca t (Fig 1) T ice in December and several times in January 1960 she had further hemoptysis In January the appearance of her chest on the x ray film was unchanged The local doctor prescribed ntibiotic cap ules and 3 grams (0 2 Gm) of thyroid daily Return of the pain and al-o sweats huskiness of the oice and increasing breathlessness so that she was a little breathless even at rest and serious loss of weight one stone (6 kilograms) 3 months led to her admission t ho pital on February 2 1960

Her previous medical history mentioned rheu matism in the right wrist at the age of 10 since when this wrist had ached a little in cold weather and also appendectomy t the age of 16 Menstrua tion as regular and normal but the last period had been a eek early and the flow scanty During her pregnancy a negativ blood Wassermann reaction had been recorded

The family history mentioned a paternal uncle ho had died *of rheumatic fever* and a sister who had died of pneumonia Her mother was under *treatment for pernicious anemia*

Examination on admission revealed n anxious young woman propped up on pillow breathing shallowly and quickl (respiratory rate of 40 per minute) Her temperature w 100 4 F (38 C) E ery now nd then she had a paroxysm of hard dry coughing which caused her pain and distress Her fingers were slightly cyanosed but there as no clubbing

Her chest movement wa diminished on the left side The breath sounds and the ocal fremitus and esonance were diminished over both lung bases posteriorly and the percussion note was impaired The chest seemed to be tender all over

The pulse rat was 130 per minut and the blood pressur was 115 75 mm Hg The pex beat of the heart was palpable in the sixth left intercostal space 3½ inches (8 cm) from the midline The heart sounds ere normal in so far one could strike out

F m h Royal N h S Hospital f Syd Syd ey Au al
Received for publ ion Aug 1 1960

Protocol d ph graphs by A Murray Ll d A tant Medical Reg tra f th Hospital Med ne D uglas J And son, Ho ora Physician Ad sser Douglas S Stuck y H orary A nt Physician Contributor James Kalok s D ect of Diagnostic Rad logy R inald G Epps Hon As tant P ici Zelm Freeman, Honorary Associate Physician E Beatrix D rie Bacteriologi Otto Kra d J hn L Raven Pa thologist K O A J nes, P thology R strar

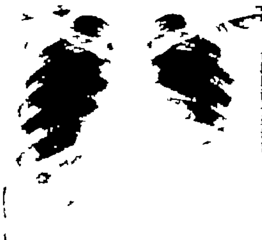


Fig. 1. X-ray film of the chest taken on Dec. 26, 1959.



Fig. X-ray film on the chest taken on Feb. 3, 1960.

but a loud crunching pericardial friction rub was audible over most of the precordium.

No other abnormalities were discovered.

The results of laboratory investigations made in the hospital at the time of admission were as follows: *Blood*: Hemoglobin, 9 Gm. per cent; leukocytes, 18,500 per cu. mm. (neutrophils 0, eosinophils 5, basophils 1, lymphocytes 14, monocytes 10 per cent). Of the neutrophils 13 per cent were band forms. Sedimentation rate was 70 mm. in 1 hour (Hawksley tube, normal 4 to 8 mm.). No lupus erythematosus cells were found. The serum protein level was 6.6 Gm. per cent (albumin 3.4, globulin 3.2, no cryoglobulin). An intracutaneous tuberculin test gave no reaction. Sputum culture grew micrococci and green streptococci. The urine contained no albumin or sugar; microscopy showed only an occasional leukocyte. The antistreptolysin O titer was 625 units per ml. X-ray examination of the chest (Fig. 2) showed slight enlargement of the heart but considerable dilatation of the left atrium; also there was hilar congestion and a little fluid at the left lung base. An electrocardiogram (Fig. 4) showed right axis shift but no other abnormality.

On February 3 the patient had a paroxysm of supraventricular tachycardia which lasted for several hours (pulse rate of 220 per minute) and which caused dyspnea and dilatation of the jugular veins. Digoxin was given in full dosage with much improvement. Two days later he was able to sit comfortably in a chair by the bedside. Over the next few days as the pulse became slower and as the pericardial friction diminished in loudness and finally disappeared, a soft systolic murmur of ejection type was heard to the left of the sternum.

On February 8, after the patient had complained of nausea for several days and had vomited, an intern reported that a mass was palpable above the pubis, but this observation was not confirmed by another examiner. A specimen of serum was subjected to the Galli Mainini toad test for pregnancy with a negative result. The same intern reported the mass again on February 19 when it was thought to be the urinary bladder.

By February 16 the patient felt much better although the temperature usually rose above 99°F (37.2°C.) in the afternoons. X-ray examination showed the heart to be a very little smaller and the lungs much less congested. However, low-pitched crepitations were audible at the left lung base. Palpation of the chest showed that the right ventricle was contracting more forcibly than normally and the pulsation of the pulmonary artery could be felt. The palpable sensation due to the closure of the pulmonary valve was closely followed by another. At the left sternal border a presystolic sound was heard and a systolic murmur of ejection type. At the mitral area a third sound was heard early in diastole. The first sound was loud and clear.

During that night further hemoptysis occurred and thence the patient's condition deteriorated with increasing hemoptysis, orthopnea, and cyanosis



Fig. 3. X-ray film of the chest taken on Feb. 24, 1960.

features of the illness which I have already stressed they appear to be predominantly respiratory certainly in the beginning and to some extent throughout the entire illness There are many pulmonary complications of rheumatism embolism pneumonitis and so on but most of those are transitory They come and go and resolution occurs or they heal and disappear Here we have the strong impression of some persistent and relentless lesion in the left lung throughout the entire course of the illness

So that brings us naturally I think to the other important path to take in trying to correlate these two approaches and that is the question of pulmonary neoplasm as the possible explanation for the general features of the patient's illness Could this be a neoplasm in the lungs left lower lobe with spread to the pleura pericardium and conceivably to the left atrial cavity with mitral valvular obstruction? We know that this may occur occasionally myxomas are the common tumors that occur in the left atrium The main argument against this suggestion is the rarity of pulmonary neoplasms in 24 year-old women and the much greater rarity of intracardiac spread of neoplasms Undoubtedly it might occur

Therefore in summation my strong feeling is that there is definite evidence of progressive mitral valvular obstruction with the late development of pulmonary hypertension and in my view this cardiac lesion was the immediate cause of death When we come to the more difficult question of underlying pathology I feel that one cannot be dogmatic There are two possibilities first progressive rheumatic carditis with mitral valvular obstruction and unusual pulmonary complications and second pulmonary neoplasm with spread to the pleura pericardium and the left atrial cavity with mitral valvular obstruction I find it difficult or impossible to decide between those two possibilities but I feel very firmly that mitral valvular obstruction was present and was the cause of death

MODERATOR Dr Kalokerinos Dr Stuckey emphasized that throughout the entire series of x ray films there was persistent abnormality at the left lung base Would you look at this film of February 13 and tell us whether in fact this lesion has persisted at the lung base or whether it has not temporarily disappeared in that film

DR KALOKERINOS The lesion at the left base has certainly not completely cleared up but it is much less distinct than in the earlier films I think that we should presume that the opacity which we see at the left base has been due mostly to effusion which has almost cleared up but that there is underlying lung disease as well

MODERATOR What about rheumatic pneumonia? Do radiologists recognize it as an entity? Would it be a possibility in this case?

DR KALOKERINOS Yes rheumatic lung is described One may see pleural effusion and areas of consolidation in the presence of rheumatic heart disease usually in its acute phase but the changes in the lung are not specific

MODERATOR One other point if you will be so kind The appearance of the right lung in the final film was described by Dr Stuckey as hilar congestion and was also reported by the radiologist in those terms Do you think that that appearance might be consistent with a pneumonic process? There was a very high leukocyte count at that stage

DR KALOKERINOS I think that it was on the day after this film was made that the patient died We are seeing a terminal phenomenon We can see that the opacity is more marked in the medial half of the lung It is not just vascular shadow The appearance in the left lung field is somewhat similar although not so well pronounced It is not possible to state just what proportion of the opacity was due to edema of the lung and what proportion to consolidation but both are present

MODERATOR Dr Epps I did not see your name associated with this patient Presumably you were not asked to perform cardiac catheterization in order to try to elucidate the cause of the mitral valvular obstruction Do you think taking into consideration this patient's pyrexia and the severity of her illness at the time that cardiac catheterization would have been either feasible or helpful?

DR EPPS I think that there would have been some risk attached to cardiac cath

place at short notice and I understand did have some knowledge of this patient's case when the autopsy was performed

DR. JONES The autopsy was carried out 25 hours after death The body was that of a slightly obese young woman There were no scars The thyroid larynx and pharynx were normal The peritoneal cavity and the abdominal viscera were normal except as I shall tell you The liver showed slight evidence of congestion but was otherwise normal The spleen was normal in size The right suprarenal gland was normal The left suprarenal gland was normal but beside it was a nodule 1 5 cm in diameter whose cut surface was homogeneous Several of the retroperitoneal lymph glands were slightly enlarged and had similar homogeneous cut surfaces The cervix and body of the uterus were normal

The tubes and right ovary were normal The left ovary was replaced by a large tumor 15 by 9 by 9 cm in size which had a lobulated appearance (Fig 6) It felt semisolid and when cut was seen to have undergone postmortem degeneration The more solid parts appeared white and homogeneous The tumor appeared to be perfectly encapsulated Its attachments were those of a normal ovary There was no involvement of the local lymph gland

The pleural cavities each contained one or two fluid ounces of a straw-colored fluid There were adhesions between the [pa]rietal and visceral pleura of the left [lung] at the apex and on the diaphragmatic [surfa]ce These were dense but of small ... There was a nodule 1 cm in diameter ... lateral surface of the lower part of ... lower lobe It was in the lung tissue beneath the pleura The esophagus ... mal At the bifurcation of the ... was a small amount of blood ... d which appeared to be coming ... the right side The left bron... ed mucoid material and had ... tely compressed by grossly ... heobronchial lymph gland ... me small nodules along the ... ymphatics The lung was ... ut but there was a small ... lower lobe There were ... the lung tissue which ... ion previously men...

There were several enlarged homogeneous lymph nodes—these were smaller than the ones on the left side The right upper lobe was normal The right middle lobe was consolidated to a moderate degree The right lower lobe was entirely consolidated and sank when placed in formalin The venae cavae were normal The pericardial cavity was completely obliterated by nodules of tissue with homogeneous surfaces Between the nodules was fibrinous material The larger nodules were situated on the left side of the pulmonary artery and immediately between the pulmonary artery and the aorta They extended into the wall of the left atrium The pulmonary artery had been moderately compressed by the tumors The left atrial cavity had been invaded by a lobulated piece of tumor which had obliterated its lumen to a marked extent and probably prevented efficient contraction This piece of tumor extended down to and just through the mitral valve The tumor which passed through the mitral valve caused some obliteration of the orifice of the valve



Fig 7 Heart laid open to display the cavities of left atrium and ventricle, showing metastatic tumor with shining surface, almost filling left atrium and extending through mitral orifice into the ventricle.



Fig 4 Uterus and adnexae showing the tumor of the left ovary

sis of mitral valvular obstruction and pulmonary hypertension due possibly either to rheumatic heart disease or to pulmonary neoplasm Dr Epps has added to that the possibility of thrombosis in the pulmonary circulation Is there anyone else who would like to make any suggestions or comments on what has gone before?

DR KRAUS We have the heart syndrome the lung syndrome and the temperature It all fits in well with mitral stenosis and superimposed bacterial endocarditis We have no result of blood cultures but we have a high antistreptolysin titer so we are able to suggest bacterial endocarditis

MODERATOR Dr Kraus has drawn attention to the high antistreptolysin titer

DR STUCKEY I found this very difficult to interpret It was done at a late stage of the patient's illness This can be a useful diagnostic test in the early stage of an illness which may be rheumatic fever Its significance is that there has recently been a streptococcal infection particularly if there is a rising titer over a few weeks The significance of this particular test which was made some 4 months after the onset of the illness I just do not understand The figure given is abnormally high but I find it difficult to place very much reliance on that test at that particular time either for or against a rheumatic etiology

MODERATOR Any further suggestions?

DR FREEMAN One of the things to be thought of is the possibility of a mycotic infection of the lungs such as by Monilia These sometimes spread from the lung to the pericardium and might perhaps affect the heart Another condition that crosses my mind is Wegener's granulomatosis or polyarteritis nodosa of the lung Whether that could cause such grave obstruction I do not know Another thing is the possibility of chorionepithelioma metastasizing to the lung and to the heart because there was a question here of a pelvic mass

MODERATOR Yes and there was an irregularity of menstruation

MR RAVEN I would like to suggest an infiltrating lesion of the mediastinum—I thought of Hodgkin's disease because the patient was a young woman and there were signs of involvement of the left atrium pleura of the left lung and pericardium Also the anemia fever loss of weight terminal leukemoid reaction and the persistent eosinophilia were suggestive of Hodgkin's disease Although there were no signs elsewhere of the disease Hodgkin's disease can remain localized to the mediastinum

MODERATOR Are there any other contributors before we call on the pathologist to tell us the answer? I am very sorry to say that Dr Colin Graham was unable to be present at this conference but Dr Jones has more than kindly taken his

place at short notice and I understand did have some knowledge of this patient's case when the autopsy was performed

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The pleural cavities each contained one or two fluid ounces of a straw colored fluid There were adhesions between the parietal and visceral pleura of the left side at the apex and on the diaphragmatic surface These were dense but of small area There was a nodule 1 cm in diameter on the lateral surface of the lower part of the left lower lobe It was in the lung tissue but just beneath the pleura The esophagus was normal At the bifurcation of the trachea was a small amount of blood stained fluid which appeared to be coming mostly from the right side The left bronchus contained mucoid material and had been moderately compressed by grossly enlarged tracheobronchial lymph glands There were some small nodules along the peribronchial lymphatics The lung was aerated throughout but there was a small infarct in the left lower lobe There were no abnormalities in the lung tissue which underlay the adhesion previously mentioned

There were several enlarged homogeneous lymph nodes—these were smaller than the ones on the left side The right upper lobe was normal The right middle lobe was consolidated to a moderate degree The right lower lobe was entirely consolidated and sank when placed in formalin The venae cavae were normal The pericardial cavity was completely obliterated by nodules of tissue with homogeneous surfaces Between the nodules was fibrinous material The larger nodules were situated on the left side of the pulmonary artery and immediately between the pulmonary artery and the aorta They extended into the wall of the left atrium The pulmonary artery had been moderately compressed by the tumors The left atrial cavity had been invaded by a lobulated piece of tumor which had obliterated its lumen to a marked extent and probably prevented efficient contraction This piece of tumor extended down to and just through the mitral valve The tumor which passed through the mitral valve caused some obliteration of the orifice of the valve



Fig 7 Heart laid open to display the cavities of left atrium and ventricle, showing metastatic tumor with shining surface almost filling left atrium and extending through mitral orifice into the ventricle

and also prevented the cusps from closing adequately. This slide (Fig. 7) shows the tumor in the atrium and projecting down into the orifice of the mitral valve. The right ventricle was slightly hypertrophied. The right atrium and the left ventricle were normal. The other valves were quite normal. The coronary arteries were normal and the aorta showed a little atheroma. The breasts were normal. The brain was not examined.

Microscopically, the ovarian tumor proved to be a very cellular sarcoma with pleomorphism of the cells and nuclei. There were areas of mucoid degeneration. The right middle lobe between areas of consolidation showed extravasation of blood into the alveoli. The right lower lobe was consolidated and appeared in the stage of gray hepatization.

The hilar and upper abdominal nodes examined showed a sarcoma similar to that in the ovary. The tumor which invaded the left atrium showed the same histologic picture, and areas of it had undergone infarction.

MODERATOR: Dr. Stuckey told us that a neoplasm within the chambers of the heart would be a rarity indeed.

DR. LLOYD: I am sure that many people would agree that neoplasm of the heart, either primary or secondary, is extremely rare, but on reviewing the literature we find that in the experience of pathologists it is relatively common. Beginning about 1856, the pathologists started reporting long series of cases in which the incidence of secondary involvement of the heart was as high as 0.5 per cent of all autopsies and about 6 per cent of cases of disseminated malignancy. The frequency with which these cases has been reported has grown. Up to 1908, 150 cases of secondary neoplasm of the heart had been reported, but in the years following 1931 there were 200 cases reported. However, they were all diagnosed postmortem, and to bear out this fact was a figure that up to 1950 only 20 cases of malignancy of the heart had been diagnosed antemortem. So I think that it is certainly excusable that in this case the diagnosis was not exactly pinpointed either while the patient was in the hospital or by Dr. Stuckey in his very good discussion of the case.

A few other points about secondary malignancy of the heart should be made. It is generally accepted that the right side of the heart is more commonly involved than the left. The reason for this appears to be that 75 per cent of the coronary arterial blood returns to the right side of the heart. The valves themselves are very rarely involved, and when they are involved do not usually cause obstruction. The endocardium is also involved rarely, and when it is it can be involved in either of two ways. As in this case, the growth may invaginate the endocardium and so have a glistening appearance. I think you will agree from the slide that this tumor was quite shiny. Then, the endocardium may receive direct deposition of tumor masses which are accordingly rough, and these may have blood clot superimposed on them and simulate very exactly subacute bacterial endocarditis. The case most closely resembling this one that I can find was reported by Wainwright in 1938. It was a case of secondary sarcoma of the lung. The growth had extended from the lung down the main pulmonary vein and had gone right through the left atrium and through the mitral valve. I could find no case in which there had been a secondary deposit causing a mitral stenotic type of lesion.

The primary site of tumors causing secondary involvement of the heart may be in any organ of the body; the most common one is the lung, and that is closely followed by the breast.

One thing which is apparent in the literature, and which is brought out very well in this case, is the extensive involvement of the heart that may occur before decompensation sets in. This girl went on for several months without a great degree of disability. Admittedly, she was a good deal restricted, but one is amazed that the heart managed to work at all when one considers all the findings which we have discussed here.

Other points that were made in the extensive available literature were that again it is an extremely difficult condition to diagnose if there is no primary neoplasm which is obvious—as in this case. It is important to bear in mind the diagnosis of this type of condition when there is un

explained heart disease with no history of rheumatic fever and no coronary disease and particularly when there is a pericarditis or pericardial tamponade or an arrhythmia of any kind or congestive cardiac failure which is progressive in spite of treatment.

Clinical diagnosis: Mitral stenosis; rheumatic carditis.

Dr. Stuckey's diagnosis: Mitral valvular obstruction and pulmonary hypertension due either to rheumatic heart disease or pulmonary neoplasm.

Other suggested diagnoses: Pulmonary thrombosis (Dr. Epps). Wegener's granulomatosis or chorionepithelioma (Dr. Freeman); subacute bacterial endocarditis (Dr. Kraus). Hodgkin's disease of the mediastinum invading heart and lung (Mr. Raven).

Anatomic diagnosis: Sarcoma of left ovary with secondary deposits in the heart obstructing the mitral valve and in the lung, pleura and tracheobronchial lymph glands; pulmonary thrombosis; pneumonia.

Annotations

Mathematical physics and the physician

One of the facts of life is that in only a few specializations among them the cardiovascular is the background of physicians in mathematics and physics totally inadequate. In most of the medical field (general practice surgery obstetrics pediatrics psychiatry the greater part of internal medicine etc.) hardly any or no mathematics at all is needed. The consequence of this is that it is impractical and certainly impossible to adapt the curriculum to the needs of the relatively small group. This is especially so since these needs are far greater than is generally realized. The only thing that could be done and which has sometimes been tried without success is to supply the needs of the small group during the time of their specialization. Why did these attempts fail in most cases? Chiefly because the problem of time involved is usually underrated by teachers and students. Because we do not like unpleasant facts we close our eyes to them. It is an unpleasant fact that nowadays for fruitful research in several medical fields a background in classic physics is needed that is equivalent to that of the well trained physicist. When the physician cannot acquire this background in a few hours he is inclined to lose courage and quit. Practically always the teacher has to try to take a shortcut and teach all the necessary mathematics in a very short time by giving a so-called *popular course* which actually is more a course in mystics than in mathematics. We need not wonder that the only result is a well-cultivated inferiority complex among the students. When the course is rigorous and good the result is nil also because our medical doctors are not mentally prepared for the amount of self study and homework that is required.

[illegible] In mathematics there is no path for kings and I would like to add not even for doctors! When a young doctor wants to specialize and do research work in the cardiovascular field he has to be prepared to follow during the first four years of his training three hours of rigorous mathematics and physics lectures per week, lectures that will require from him at least 2 hours of intensive homework per day, weekends not excluded! How this has to be fitted into his schedule is his problem and that of the chairman of the department. It is a pity if this problem cannot be solved, for then we have to be satisfied to gradually leave more and more of our research to physicists who are willing to spend an equivalent amount of time acquiring knowledge in the cardiovascular field. Teamwork between a physician who knows nothing about physics and a physicist who knows nothing about medicine may seem an attractive substitute but it does not work. Team workers have to understand each other's language and problems thoroughly. Our young cardiologists have to take the whole dive into the mathematical ocean; just dipping their big toe into the water will not be sufficient.

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Etiology of pre-eclampsia eclampsia

The etiology of specific hypertensive disease of pregnancy has long remained an enigma. Although eclampsia has been recognized as a clinical entity from antiquity, the primary pathogenetic factor has escaped detection despite extensive clinical study. During the nineteenth century eclampsia was erroneously regarded as a form of Bright's disease, as a primary disease of the liver, and even as a condition comparable to parturient paresis in cattle. The latter concept led to the practice of mastectomy as a therapeutic measure as advocated by Sellheim. With the development of a satisfactory practical technique for measurement of blood pressure at the turn of the century, pre-eclampsia was recognized as a hypertensive state preceding the development of convulsions or coma. Subsequently Volhard in 1918 properly emphasized the primary vascular nature of pre-eclampsia eclampsia. However, until recent years a confused state of affairs relative to etiology and diagnosis persisted as evidenced by

the inclusion of acute yellow atrophy of the liver, pernicious nausea and vomiting, various renal affections as well as certain hypertensive states peculiar to pregnancy in the category of toxemia. In clinical thinking the etiological factor common to these various entities was considered to be a toxic material (hence toxemia), a concept culminating in the studies of the Smiths concerned with the identity of such a substance which presumably was elaborated because of errors in hormone metabolism.

A number of authors including Bartelmez, Brust and co-workers, Kellar and Sutherland have suggested that a pressor substance was responsible for the vascular phenomena basic to the toxemic complex. The possible relation of placental ischemia to the production of a humoral agent has been discussed by Page but the identity of such a compound or isolation of a pressor material from pregnant animals or the products of conception has been notoriously unsuccessful. However, the recent observations of Hunter and Howard indicate that such a pressor material may be consistently isolated from the decidua and amniotic fluid of patients with toxemia but not from normal pregnant subjects. These findings, if confirmed, may represent a most significant contribution to our understanding of the pathogenesis of acute toxemia of pregnancy.

Hunter's active material has been termed hysterotonin. Preliminary studies suggest that it is a polypeptide of large molecular size, the activity of decidual extracts not being decreased by dialysis. It is lacking in antidiuretic activity and is apparently distinct from angiotonin as well as other polypeptides which produce pressor responses. The active principle is thermostable between pH 3.3 and 8.3 and is rapidly inactivated by kidney extracts, but the pressor activity is potentiated by incubation with plasma. The authors suggest, on the basis of their experimental observations, that hysterotonin is produced by an enzymatic reaction according to the following scheme: Enzyme (in decidua) + Protein (in plasma or amniotic fluid) → Hysterotonin.

In consideration of the many disappointments of the theorists over the years concerning the etiology of the specific hypertensive diseases of pregnancy, optimism must be guarded in acceptance of new data bearing on this problem. However, it is hoped that the chemical characterization as well as the kinetics of production of Hunter's pressor substance will be forthcoming with continued investigation of what may historically be regarded as a major contribution to reproductive research.

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REFERENCES

1. Bartelmez, M. A., van B., and Mastboom, J. L.: Ischaemia of the gravid uterus, a probable factor in the causing of toxaemia. Toxaemias of pregnancy, Philadelphia, 1950, Blakiston.
2. Brust, A. A., Assali, N. S., and Ferris, E. B.: Evaluation of neurogenic and humoral factors in blood pressure maintenance in normal and toxemia pregnancy using tetraethylammonium chloride, J. Clin. Invest. 27: 717, 1948.
3. Hunter, C. A., Jr., and Howard, W. F.: A pressor substance (hysterotonin) occurring in toxemia, Am. J. Obst. & Gynec. 79: 838, 1960.
4. Kellar, R. J., and Sutherland, J. K.: Renin and pregnancy, J. Obst. & Gynaec. Brit. Emp. 48: 487, 1941.
5. Page, E. W.: Placental dysfunction in eclamptogenic toxemias, Obst. & Gynec. Surv. 3: 615, 1948.
6. Sellheim, H.: Die mammäre Theorie über die Entstehung des Eklampsiegiftes, Zentralbl. f. Gynäk. 34: 1609, 1910.
7. Smith, J., van S., and Smith, O. W.: Internal secretions and toxemia of late pregnancy, Physiol. Rev. 28: 1, 1948.
8. Volhard, F.: Die doppelseitigen hämatogenen Nierenerkrankungen, Berlin, 1918, J. Springer.

Steroid maintenance treatment in cor pulmonale

Although antibiotic therapy has reduced the hazards of acute infection in patients with chronic bronchitis and asthma, it has, by prolonging their lives, encouraged an increased incidence of chronic cor pulmonale and the prospect of progressive invalidism.

Experimental, pathologic, and clinical evidence[1-4] indicates that two basic mechanisms acting alone or in combination are responsible for this cardiac disability: (1) alveolar hypoventilation with anoxia and hypocapnea inducing pulmonary vasoconstriction, hypervolemia, and increased cardiac output and (2) anatomic reduction of the pulmonary vasculature. The evidence also suggests that the former is probably the more important mechanism.

Thus acute bronchial infection and emotionally induced asthma disorders more likely to aggravate anoxia than to accentuate vascular damage, frequently precipitate congestive failure in patients with chronic cor pulmonale, and the absence of cor pulmonale in patients after pneumonectomy indicates that pulmonary vascular destruction must be extensive before it contributes to the development of this condition. Furthermore,

patients dying w th cor pulmonale often ha com paratively little destruction of lung asculature but prominent signs of re piratory obstruction in the form of bronch tis bronchioliti and broncho pneumonia.

Such evidence however does not exclude the functional effect of increased intra alveolar pressure emphysematous subjects when communicated to the pulmonary capillaries this increased pressure raises pulmonary vascular resistance nd elevates pulmonary arterial pressure Nor do pathologic changes take into account the respiratory pump which influences pulmonary arterial pressure by ary ng the stroke output of the right entricle in this respect wide fluctuations in pulmonary arterial pressure associated w th increased respir tory excursion hav been reported in patients with chronic pulmonary heart disease

The reversibility of the pulmonary hemodynamic consequences of anoxia by adequate oxygenation fa ors the iew that anoxia is of major importance *in the development of cor pulmonale* nd emphasizes that relief of anoxia must be the prime consideration in the treatment of this condition Requirements for oxygen can be reduced with bed est and anti thyroid drugs and oxygenation improved by main ta ning free airw y w th ant pasmodics and expectorants combined w th antibiotic treatment These measures may be supplemented by inter mittent oxygen ther py and when heart failure is present by digitalis diuretics nd salt restriction also Venesection t reduce the hematocrit lev l to between 45 and 50 per cent w thout lowering the hemoglobi below 12 Gm per cent may be of some lue Sed tion hould be avoided because t en courages anoxia

Steroid drugs might be expected to benefit asth matic patients w th cor pulmonale since a well as increasing oxygenation by improving pulmonary entilatory capacity they will relieve acute asth matic ttacks an l by thus correcting acut noxia and simultaneously reducing respiratory efforts they ould remov two of the major factors pro moting pulmonary hypertension Furthermore the ability of long term steroid therapy to prevent or to greatly reduce the frequency and severity of acute asthmatic episodes in patients with ch onic asthma [12] suggests that this treatment might pre vent or delay the development of cor pulmonale in such patients

Although steroid drugs have been advocated in the treatment of chronic cor pulmonale [13] some[6] consider the benef ts to be out eighed by the pos ble a l erse side effects [12] especially when usage is continued for long periods.

That long term steroid therapy may be of alue in certain patients with cor pulmonale is evident from a recent report [14] Four patients w th bronchial asthma received prednisolone for periods which aried from 9 t 18 months 3 of the patients had clinical and electrocardiographic evidence of chronic cor pulmonale and 2 of these were in heart fa lure when steroid treatment w started The symptomatic relief induced by this treatment w s ma tained in these 3 patients whose exercise tolerance was so improved that each was able to lead normal lif of unrestricted activity N less gratifying was the objective improvement coexistent heart failure promptly subsided (in one case congestive failure was resistant to standard treatment) rhonchi dis appeared nd n each instance the abnormal elec trocardiographic patterns reverted to normal

Patients in this series also had certain features which suggested state of adrenocortical insuf ficiency and this clinical premise was supported by biochemical evidence which further indicated that such insufficiency was due to decreased activity of the anterior pitu tary gland It was argued there fore that in add tion to the reasons already ad anced in fa or of long term steroid therapy such treatment as substitution therapy was indicated these patient i order to correct an endogenous deficiency This reasoning was fa ored by the fact that improvement w s achieved and maintained by physiologic (prednisolone 7 5 to 12 5 mg daily) rather than pharmacologic dosage nd perhaps also by the diuresis[14 15] which the patients exh bited and which has previously been reported in asthmatic patients[16] *during teroid treatment*

As might be expected with physiologic teroid dosage adverse side effects did not occur the dosage was increased by 5 mg daily during intercurrent infection and the patients were warned that extra steroid would be necessary w th expert super ision should they be exposed to particular haz ards—for example general anesthesia

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REFERENCES

1. Ferrer M I Harvey R M Cathcart R T Webster C A Richard D W and Cournand A Some effects of digoxi pon the heart and circulation in ma Digoxin n chronic cor pulmonale Circulation 1 161 1950
2. Lavenne F Le retentissement cardio-vascu laire de la silicose et de l anthraco silicose Contribution à l étude du cor pulmonale Extrait de La Revue Belge de Pathologie et de Medecine Experimentale Acta med belg 21 Suppl 6 1951
3. Ferrer M I and Harvey R M Decompen sated pulmonary heart disease with a note on the effect of digitalis *I* Pulmonary circul tion edited by W R Adams nd I Veith New York 1959 Grune & Stratton Inc
4. Harvey R M and Ferrer M I A clinical con ideration of cor pulmonale Circulation 21 236 1960
5. Rodbard S Karas I and Heiman D F The diagnostic significance of the re piratory fluctuations of the pulmonary arterial pressure in man AM HEART J 51:182 1956
6. Thursby Pelham D C and Kennedy M C S Prednisolone compared with cortisone in treatment of children with chronic asthma Brit M J 1:243 1958
7. Lowell F C Schiller I W Leard S F nd Franklin W Prolonged treatment of bronchial asthma with cortisone J Allergy 24:112 1953
8. Savidge R S and Brockbank W Long term control of severe bronchial asthma with oral cortisone Lancet 2:889 1954
9. Davies B M and Williams D A Use of

corticotrophin gel and cortisone i treatment of severe and intractable thma Brit M J 2 293 1953

10 Brown H M Treatment of chronic asthma with prednisolone significance of eosinophils in the sputum Lancet 2 1245 1958

11 Phear D Ball K and Page F Prolonged treatment with steroids in severe chronic a thma Lancet 1 139 1960

12 Hickam J B and Ross J C Respiratory acidosis in chronic pulmonary heart disease Pathogenesis clinical features and management Prog Cardiovas Dis 1 309 1959

13 Arbesman C E and Ehrenreich R J Meti corten and 9 alpha fluorohydrocortisone in treatment of allergic disorders J Allergy 26 189 1955

14 Barach A L Bickerman H A and Beck G J Clinical and physiological studies on use of Metacortandracin in respiratory dis ease bronchial asthma Dis Chest 27 515 1955

15 Mickerson J N Prednisolone maintenance therapy in chronic pulmonary heart disease Brit Heart J 22 220 1960

16 Mickerson J N nd Swale J Diuretic effect of steroid therapy obstinate heart failure Brit M J 1 876 1959

17 Mickerson J N A tenor pituitary deficiency in disorders associated with steatorrhoea Brit M J 1 379 1960

18 Bickerman H A Beck G J nd Barach A L Use of prednisone (Meticorten) in re spiratory disease pulmonary emphysema and pulmonary fibrosis J Chron Dis 2 247 1955

Masked thyrotoxicosis and coronary artery disease in father and son

A familial factor is common in many constitutional diseases Sometimes this is quite strong and dominant and at other times it is less impressive Hyper thyroidism belongs to the latter type The same is true of coronary artery disease There certainly are families that ha e more than their share of angina coronary thrombosis or sudden unexpected deaths It is also true that relative antagonisms exist between one disease and another I the pre liver days it was extremely rare to see hypertension in patient w th untreated pernicious anemia Coronary thrombosis is less common in patients w th alcoholic cirrhosis than in the general popula t on at the same age level Likewise angina pectoris or coronary thrombosis is comparatively rare in those who have hyperthyroidism t the same time This does not mean that the tw states do not occur together I hav seen small number of such cases but in an extensiv experience with coronary disease the simultaneous presence of both coronary di ease and hyperthyroidism has not been frequent

Many years ago (Dec 27 1928) I examined 52 year-old man who complained of pain in the right anterior chest coming t rest and on effort lasting several minutes or even as long as one half hour and at times radiating down both arms This began about 2 months previously and had been growing orse He as sent to the hospital for more careful observation Because of the appearance of the face (salmon-colored skin) unilateral stare and an unexplained insidious loss of 35 pounds of weight during the previous months I su pected that he had hyperthyroidism The basal metabolic rate was +45 per cent Because he had no exophthalmos or palpable thyroid gland nd had regular heart rate of 70 or less neither the physicians on the medical service nor the surgeons would accept th diagnosis of hyperthyroidi m He was thought to ha e suffered coronary thrombosis during the early day of the hospitalization because of a slight fever nd leukocytosis and definite transient inversion of the T wa in Lead I of the electro cardiograms (only three leads were taken in 1928) H continued t h anginal ttacks at rest in bed which were promptly relieved by nitroglycerin until he was given course of Lugol solution The angina then promptly improved but did not disappear entirely I had no doubt about the diagno sis of thyrotoxicosis all this time He was then given course of x ray treatment over the thyroid region the Lugol solution was discontinued and he was discharged to the outpatient heart clinic However the anginal state grew orse nd he was sent into the surgical service for a subtotal thyroidectomy Immediately after this operation the angina anished and he carried on satisfactorily He died 17 years later in 1945 at the age of 69 years

Thirty-one years after the abov mentioned experience (Dec 26 1959) I saw another patient in neighboring hospital who complained of pain to the right of the mid-sternum This was choking sensation hich came on generally t rest and often radiated into both arms and hands He was given digitalis by one physician which made the condition orse The spells were helped by nitroglycerin. Sometimes he would use about 20 nitroglycerin pills during the day and 10 t night Ordinary physical examination was entirely negativ Without any knowledge of the events soon to be described I noted that the patient had peculiar salmon colored skin and I therefore thought about the possibility of hyperthyroidism It then occu

to me that the patient's name was familiar to me. It developed that he was the son of the man whom I had examined 31 years before, whose history was discussed above. Here we had father and son with the same condition. As in the first case, it was also difficult to convince his physician that we were dealing with masked thyrotoxicosis. Some days thereafter he suffered a definite coronary thrombosis from which he recovered. The laboratory data supported the diagnosis of thyrotoxicosis. The blood cholesterol was 140, the radioactive iodine uptake was 59 per cent, the red blood cell radioactive iodine uptake was 23.8 per cent (normal = 14-18 per cent), protein-bound iodine was 16.0 micrograms per cent, and the basal metabolic rate was +17 per cent. He was later given 5 millicuries of radioactive iodine, and he made an excellent recovery.

Father and son had a similar and uncommon combination of conditions. They both had masked hyperthyroidism and angina pectoris. In both the pain was in the right rather than in the left chest. In both instances it was not easy to convince the attending physicians that thyrotoxicosis was present because exophthalmos was absent and a palpable thyroid gland could not be made out. A clue to the diagnosis was the peculiar salmon-colored appearance of the skin of the face. Finally, in both instances dramatic improvement in the angina resulted on appropriate treatment for the thyrotoxicosis.

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REFERENCES

1. Morrison, H.: The familial incidence of exophthalmic goiter, New England J. Med. 199:85, 1928.
2. Howell, W. L., and Manion, W. C.: The low incidence of myocardial infarction in patients with portal cirrhosis of the liver. A review of 639 cases of cirrhosis of the liver from 17,731 autopsies, Am. Heart J. 60:341, 1960.
3. Littman, D. S., Jeffers, W. A., and Rose, E.: The infrequency of myocardial infarction in patients with thyrotoxicosis, Am. J. M. Sc. 233:10, 1957.
4. Levine, S. A., and Walker, G. L.: Further observations on latent hyperthyroidism masked as heart disease; angina pectoris, New England J. Med. 201: No. 21, pp. 1921-1930, Nov. 23, 1929 (Case 9).
5. Somerville, W., and Levine, S. A.: Angina pectoris and thyrotoxicosis, Brit. Heart J. 12:245, 1950.

Book reviews

SURGERY OF THE AORTA AND ITS BRANCHES. By James D. Hardy, M.D., M.S. (Chem.), F.A.C.S., Professor and Chairman, Department of Surgery, University of Mississippi Medical Center, and Surgeon in Chief to the University Hospital; Chief Surgical Consultant, Veterans Administration Hospital, Jackson, Miss. Philadelphia, 1960, J. B. Lippincott Company. 386 pages. Price $6.50.

A series of articles on acquired diseases of the aorta and its branches appearing in the *American Practitioner and Digest of Treatment* serves as the nucleus for this volume. The intent of this book then is to offer additional familiarity and information regarding diseases of the aorta and peripheral arteries to physicians engaged in the general practice of medicine and surgery. The various chapters, therefore, are particularly informative with regard to diagnosis of arterial diseases and indications for surgical treatment. Controversial aspects concerning the kind of surgical treatment which should be employed are largely avoided. The chapters on diseases involving the arterial supply to the upper extremities and on peripheral arterial embolism are especially interesting and informative. This book would probably not be sufficiently detailed for use by a specialist in the field of arterial diseases but does serve as a worth while source of information for those segments of the medical profession to which it is specifically directed.

NATURE OF RHEUMATIC HEART DISEASE. WITH SPECIAL REFERENCE TO MYOCARDIAL DISEASE AND HEART FAILURE. By George E. Murphy, M.D., Department of Pathology, the New York Hospital-Cornell Medical Center. Reprinted from *Medicine*, Volume 39, Number 3, September, 1960. Baltimore, 1960, The Williams & Wilkins Company. 343 pages, 147 photomicrographic illustrations in color. Price $3.50.

The basic theses of this monograph are that rheumatic heart disease in man is not a collagen disease but a heart muscle cell disease and that the involvement of the myocardium is a strong contributing if not the main cause of death in this disease in children and adults.

These theses are arrived at by histopathologic study of the disease in the entire heart and in left atrial biopsies in man and by an experimental production and histopathologic study of a rheumatic-like disease in random and specially bred rabbits. The disease in rabbits was produced by repeated focal cutaneous infection with different types of Group A beta hemolytic streptococci at monthly intervals for 6 months or a year. Some rabbits developed dyspnea, leukocytosis, rapid irregular pulse, and raised sedimentation rate and died within 4 to 14 days. In these rabbits endocardial and myocardial lesions were produced which the author believes bear a striking histological and cytological resemblance to those of rheumatic heart disease. The author brings evidence that these Aschoff-like bodies originate and evolve from rheumatic injury to heart muscle cells and not from injury to connective tissue. From a study of both human and animal material he believes that he has evidence for the origin of Aschoff bodies from myocardial muscle cells and from smooth muscle cells of the endocardium, valves, and intramyocardial coronary arteries. From study of the lesions in atrial biopsies he finds close correlation between the occurrence of specific rheumatic lesions in the atria and the presence of Aschoff bodies in the ventricles. Thus he believes that active rheumatic myocardial disease in man is an important factor in all ages for the embarrassment of cardiac function and heart failure.

The author presents an excellent review of the literature on the nature of rheumatic fever, the Aschoff body, and the experimental production of rheumatic-like disease in animals. He devotes considerable space to the difference of opinion between Saphir and himself as to whether the lesions produced by him experimentally are truly Aschoff bodies and as to whether these bodies originate from myocardial muscle cells. One hundred sixty-two exquisite photolithographs document the presentation.

This monograph is a must for all those interested in heart and collagen disease. It would appear that the author has produced a disease in rabbits which closely resembles rheumatic fever. In view of the criticisms of Saphir, it would also appear that the thesis that the Aschoff body originated from myocardial and smooth muscle cells of the heart requires further study.

RESUSCITATION OF THE NEWBORN INFANT: PRINCIPLES AND PRACTICE. Edited by Harold Abramson, M.D., Professor of Clinical Pediatrics, New York Medical College, New York; Director of Maternal and Child Health Program, New York Medical College-Metropolitan Medical Center, New York; Attending Pediatrician, Flower and Fifth Avenue Hospital, New York; Visiting Pediatrician, Metropolitan Hospital; and Chief Communicable Disease Service, Metropolitan Hospital, New York; and formerly Epidemiologist, Bureau of Preventable Diseases, New York City Department of Health. St. Louis, 1960, The C. V. Mosby Company. 274 pages. Price $10.

This is an excellent book for all who are concerned with the newborn infant and his problems of survival. The book could be better titled *Pathophysiology of the Newborn* with an emphasis on the respiratory system, and it represents the most up-to-date collection of knowledge of the many variants that influence the infant in the critical hours before, during, and after birth that has been assembled. Its strength is mainly in

ability of the contributors ll of whom are among the best in their respect e field and in the limita ion of their presentation t areas with which they are quite familiar with little pecula tion others Each contributor has documented the facts as w l as them what to do with the fact about each case as it presents and what to expect—with ery little theorizing particularly in areas of interest that are ot their ow For this they are to be commended The contributions from obstetricians are well made and are pleasing also the knowledge that pregnancy and delivery are ucces ful only if the infant lives and does well is a concept that took too long to become fact

The section on *Standard* Terminology that ppears in Chapter One and an excellent Glossary are items that are absolute neces ities for a publication of this type and the contributors ha e been uniform in their references The use of tatis tics is good—not overbearing just in formative Each chapter has comprehensive bibliography to itself which will make the book a ery useful guide

I ummary this is well written book that well edited terminology is defined from the beginning the contributors are well ch sen The major criti m would be of geographical selec tion f contributors—others in other parts of the world are also working in this field To quot from the preface, *The Concept that is advanced is fetal*—it is and t is well d ne

DIE ODEME PHYSIOP THOLOGIE UND THERAPIE DER SALZ UND WASSERRETENTION By Frv Dor Dr Jean Fabre Genev with the cooper tion of Dr Andrea Fancom and Dr Martin Rothlin with a foreword by Prof Dr Rene S Mach Genev Original in Fren h German translation by Dr A Fancom and Dr M Rothlin Basel 1960 Benno Schw be & Company 304 pages Price cloth Sw F 38 (Sole U.S and Canadia representative Intercontinental Medical Book Corp 381 Fourth A New York 16 N Y)

The authors goal in this book is to urvey and summarize th experimental nd clinical findings in research edema and salt and water metabolism and to draw pertinent physiologic path ophy iologic and therapeutic conclu ions The book is divided into three parts

The fir t part gives clear picture of the present knowled of salt and w ter metaboli m The influence and importance of antidiuretic hormone aldosterone kidney function nd hemo dynamic factors on salt and w ter metabolism and intracellular and extracellular fluid com partment are discussed

The second part deals with the pathophy ology of the numerous types of edema of different pathogenesis including cardiac, renal hepatic endocrine iatrogenic pregnancy malnutrition flammatory allergic enous nd lymphatic edemas

I the third part the therapeutic pos ibilities and problems are evaluated Th alues of salt free diet cation exchange resins usual diuretic agents paracentesis adrenal steroids phlebot omy and artificial dialysis are discu sed The aldosterone antagonist were not included

The book adequately survey many of the most recent areas in research on salt and w ter metabolism The material is presented with clarity nd in an easily understandable form The book sh uld be of value particularly to th se wh are interested in the problems of salt and w ter metaboli m

QUANTITATIVE VECTORELECTROCARDIOGRAPHY By Louis Bernberg M D Division of Cardiology Department of Medicine The Mount Sinai Hospital of New York Baltimore 1960 Waverly Press Inc 123 pages Price $5 25

This book represent a compilation of several rticle published separately by the author The chapter headings reveal the essential content of the book I The Orthovectorcardiogram A Record of Magnitude nd Orientation of the Instantaneous Forces of the Cardiac Cycle II Spherical Vectorcardiography The Use of a Sphere to Determine Angles Planes Rotation Velocity and Tortuosity III The Electric Axis nd Ventricular Gradient as Determined From the Twelv Lead Electrocardiogram IV The QRS-T Angle as Determined From the Twel Lead Electrocardiogram V A Three Dimen sional Statistical Technique Its Application to the Ventricular Gradient VI The Ventricular Gradient VII A Rapid Meth d of Determining Space Polar Coordinates

The book is profusely illustrated and should be helpful t a yone working in the field of ectorcardiography particularly if he has had little or no formal training in analytic geometry

The uthor tacitly assumes that the electrical forces generated by the heart can be represented if they were produced by a single dipole fixed in location The justification for pplying the precise quantitative methods described in this book to measurement based on such dipole concept is questionable

DIE AKUTE ARTERIENVERSCHLUSS DER EXTREMITÄTEN (EMBOLIE — THROMBOSE — PSEUDOEMBOLIE) DIAGNOSE UND THERAPIE By A Kappert Bern and Stuttgart 1960 Hans Huber Verlag 175 pages Price DM 34

In spite of the relatively small size of this vol me it is a rather comprehensive text on acute oc clu ion of arteries in the extremities including pathophysiology etiology clinical ymptoms diagnosis and therapy with 631 bibliographical references Acut arterial occlusion of partic ular clinical interest because of the need for immediat therapy Con iderable space is de voted t drug therapy (anticoagulants strepto kinase pla min activation of fibrinolysin) However statistical comparison between the

results of conservative and surgical treatment of peripheral emboli is difficult and individual prognosis is not possible (p 69) Among the objective diagnostic methods examples of continuous recording of skin temperature (Figs 3 and 4) and of Gesenius double oscillography (*Deutsche med Wochenschrift* 74 1 1949 Fig 5) before and after surgical treatment are given The resulting improvement of peripheral circulation in these examples is dramatic Winsor s segmental plethysmography (*Angiology* 8 87 1957) and rheography (impedance plethysmography) are also recommended Although peripheral arterial occlusion is the main topic naturally the discussion of pathology etiology and therapy includes related aspects of heart disease and thrombosis and embolization in other vascular regions Of interest is the differentiation of pseudoemboli (acute spastic arterial occlusion) from true peripheral thrombosis or emboli (pp 118 136) Collateral arteries of the extremities are shown in Figs 16-20 (Appendix)

Announcements

The University of Colorado School of Medicine announces the COCHEMS COMPETITION, funds for which were provided in the will of the late Mrs. Jane Nugent Cochems. A prize of $2,500 will be awarded to the author of the best paper on the subject of "The Diagnosis, Etiology and Treatment of Thrombophlebitis." The competition is open to all physicians and entries must be received in triplicate on or before Oct. 1, 1961.

The Colorado National Bank of Denver, Trustee under the will of Jane Nugent Cochems, has requested the Dean of the University of Colorado School of Medicine to conduct the competition. The judges appointed by him are Dr. Michael E. DeBakey, Professor and Head of the Department of Surgery, Baylor University College of Medicine and Dr. Sol Sherry, Professor of Medicine, Washington University School of Medicine.

Papers submitted in the competition may not be published until after the winner of the competition has been announced. At that time the winning paper and all others may be published at the discretion of individual authors. It should be noted, however, that those involved in conducting the competition will not assume any responsibility for submitting manuscripts for publication nor for any costs incident thereto. The winning paper if published must carry the designation "Awarded the Jane Nugent Cochems Prize."

Questions regarding the competition and all manuscripts should be directed to Dr. Robert J. Glaser, Vice President for Medical Affairs and Dean of the University of Colorado School of Medicine, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 20, Colo.

THE SUB-BOARD OF PEDIATRIC CARDIOLOGY of the American Board of Pediatrics announces that its organization is complete and that it is now ready to accept applications for certification both on record and by examination. The former must be submitted by Dec. 1, 1961.

Applications for approval of residency training programs in pediatric cardiology will also be accepted.

Full information and application forms may be obtained from The Executive Secretary, American Board of Pediatrics, 6 Cushman Road, Rosemont, Pa.

The members of the Sub-Board of Pediatric Cardiology are James W. DuShane, Chairman, Rochester, Minn.; Forrest H. Adams, Los Angeles, Calif.; Edward C. Lambert, Buffalo, N. Y.; Alexander S. Nadas, Boston, Mass.; Saul J. Robinson, San Francisco, Calif.; and Helen B. Taussig, Baltimore, Md.

A COURSE IN ELECTROCARDIOGRAPHIC INTERPRETATION for *graduate physicians* will be given at the Michael Reese Hospital by Louis N. Katz, M.D. and Alfred Pick, M.D. (respectively Director and Associate Director of the Cardiovascular Department) and Associates. The class will meet daily from 9:00 A.M. to 5:00 P.M. July 17 through July 29, 1961.

Further information and a copy of the lecture schedule may be obtained upon application to Miss Beverley Petzold, Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital and Medical Center, Chicago 16, Ill.

The Fifth International Congress of THE INTERNATIONAL CARDIOVASCULAR SOCIETY will be held in Dublin, Ireland, at the University College, September 7-9, 1961.

For further information contact the Secretary General, The International Cardiovascular Society, 715 Park Avenue, New York 21, N. Y.

THE AMERICAN COLLEGE OF CARDIOLOGY will hold its Tenth Anniversary Convention at the Biltmore Hotel, New York, on May 17-20, 1961, according to an announcement by Gabriel F. Greco, M.D., Ozone Park, N. Y., Chairman, Public Relations Committee. William Bennett Bean, M.D., Iowa City, will deliver the Memorial Lecture in honor of Franz Groedel, M.D., Founder and first President of the College, in the Empire City, the birthplace of the College. The tenth President of the College, Dr. Louis F. Bishop, New York, will confer on Dr. Bean the Groedel Medal for 1961. George W. Calver, Washington, D.C., is Chairman, Convention Committee. J. Maxwell Chamberlain, M.D., New York, is in charge of local arrangements. George C. Griffith, M.D., Los Angeles, Calif., is the Chairman of the Scientific Program. The scientific sessions will feature symposia on the latest achievements in cardiology and include, among many topics, problems in cardiovascular management with relation to coronary and cerebral circulation, use of anticoagulants, fibrinolysins, monoamine oxidase inhibitors, digitalis, diuretics, surgery with valve prosthesis in aortic and mitral stenosis and insufficiency, instrumentation in surgery, isotope renogram, aorto-renal arteriogram, renal function tests, critical review of latest problems in congenital heart disease and cardiac metabolism. There will be fireside conferences, exhibits and a motion picture program.

For details write to P. Reichert, M.D., Executive Secretary, American College of Cardiology, Empire State Bldg., New York, N. Y.

THE LIFE INSURANCE MEDICAL RESEARCH FUND has announced the appointment of William A. Jeffers, M.D., as Scientific Director. The appointment was effective as of April 15, 1961.

The new address for the offices of the Fund is 1030 East Lancaster Avenue, Rosemont, Pa.

American Heart Journal

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Editorial

Management of the nephrotic syndrome

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The use of corticosteroids has brought radical changes in the management of the nephrotic syndrome in the past 10 years. The physician who pushes these preparations diligently may expect diuresis in as high as 90 per cent of the victims of nephrosis and may expect the majority to have a substantial reduction in albuminuria. In roughly 10 per cent of the patients the urine will become free of albumin and remain so after a 10 to 12-day course of corticosteroids. There is no evidence at present, and no evidence can be expected from the therapy of patients, that treatment alters the underlying tendency for the disease to return. The course of the nephrotic syndrome is so variable and the treatment varies so much from patient to patient that it seems unlikely that any physician can even hope to learn the answer to this question. There is general agreement that we are keeping patients from dying from renal failure.

This is a serious disease with a 3 year mortality rate of about 30 per cent and a 4 year mortality rate of roughly 40 per cent in the 500 cases reported by Riley. Some of these patients had been treated sporadically for the elimination of edema only. Since the present treatment with corticosteroids was begun, the 3 to 4 year mortality rate has been reduced in some small series to 0.8 per cent. Treatment has varied so much from group to group that the true mortality rate is difficult to ascertain, but no authority seems to question that at least death has been deferred.

Complications of prolonged therapy constitute a serious objection. Daily continuous administration in high dosage may cause loss of protein matrix with collapse of one or more vertebral bodies. This happened to one of our earlier patients. Bilateral cataracts, with loss of all but the perception of light, has been observed by the author, and less complete lenticular opacities have been reported by others. Short term high dosage (400 to 1,000 mg. of cortisone) therapy has been accompanied by symmetrical bilateral aseptic necrosis of the femoral heads[1] in patients who were being treated for dermatological conditions. The author has had a patient on low-dosage therapy (4 to 6 mg. of methylprednisone for most of the time) for 9 years for disseminated lupus. This patient developed bilateral aseptic necrosis of the femoral heads after 6 years, which was thought to be caused by her lupus. After 8 years bilateral aseptic necrosis of the mandibular condyles occurred. No other such case has been reported, but the symmetry is so striking that the resemblance to the high-dosage cases cannot be denied, although lupus alone can

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same thing The other complications are more common and familiar Cushing s disease susceptibility to infection especially breakdown of tuberculosis and perhaps dissemination of varicella masking of pain and signs of infection duodenal ulcer acne and other less serious phenomena Hypertension occurs more frequently during the treatment of the nephrotic syndrome than during that of most other conditions and may become a seriously limiting factor to treatment Awareness of these complications often suggests remedies for them Fortunately aseptic necrosis and extensive formation of cataracts are infrequent although minor cataracts are fairly common

Since plans of treatment are varied and general agreement has not yet been reached as to which is best it may be well to summarize a statement by Conrad Riley with which all members of the National Nephrosis Foundation were in agreement (1) Corticosteroids should be given in large dosage as quickly as a diagnosis of nephrosis is made (2) The preparation to be used seems to depend on personal preference (3) Initial treatment should be continued for a long time long enough to return the patient if possible to a relatively normal state with regard to all the available measurements (4) After the initial treatment some long term plan should be made for either re treatment or continued treatment Some give steroids continuously gradually reducing the dose others wait for signs of relapse (5) All agree that proteinuria and not edema should be the determining factor in the decision to resume treatment

The choice of steroids as mentioned above is a personal matter Lange[1] treated 60 nephrotic patients with triamcinolone and was impressed with the improvement in response over results with cortisone in the same patient Two of his patients experienced marked weakness of the quadriceps muscles and of other leg muscles This persisted long after therapy was discontinued and has persuaded him to abandon triamcinolone in the prolonged continuous treatment of nephrotic patients

Daily treatment produces quicker improvement[8] but treatment with twice the dose on 3 consecutive days each week is safer Therefore most authorities prefer to give either 5 weeks of continuous therapy or continuous therapy until the urine has been albumin free for at least 2 weeks whichever is the shorter period Steroids are then withdrawn and if the patient relapses he is placed on corticosteroids for 3 consecutive days a week Believing that the smaller the amount of corticosteroids used the better the author always tries a 12 day course of therapy and if the patient s urine becomes free of albumin and remains so no further treatment is given This has occurred in about 10 per cent of the patients in some series If relapse occurs 3 to 5 weeks of daily therapy are given and then the patient is switched to administration of the steroid for 3 consecutive days a week with twice the dose Lange arbitrarily continues this for a year Heymann continues for 2 to 7 months depending upon the response of the patient Our practice has been to cut the dose in half after a month of albumin free urine cut this in half after another month and discontinue usage after another month In some patients we have maintained the same dose but dropped administration of it to 2 days a week for a month then 1 day then off Lange at one time used the latter method and believed that it was the better one The author has had too few cases to be able to judge Many relapses occur with either method Relapses require a trial first of 3 day therapy but if the condition is severe or if the patient does not respond a return to daily therapy may be necessary If there is no response after the first 5 weeks of daily treatment the patient is usually changed to 3 day therapy anyway Response should be judged by the quantitative 24 hour excretion of albumin

Dosage

Dosage is varied rather arbitrarily Five tablets (4 mg tablets of methylprednisone 25 mg tablets of cortisone) for younger children up to twelve tablets a day for adults in the 3 day treatment and one half to three fourths as much in the daily treatment are employed Our patients or their parents are taught to check the patient urine for albumin daily and they continue to do so until the urine has been free of albumin for a year This creates a certain amount of anxiety but also allays a

great amount. It has the advantage of bringing the patient back to the doctor promptly if relapse occurs.

Luetscher[3] has pointed out the advantage of checking the blood sodium of the severely edematous subject prior to treatment and suggests giving salt poor albumin if the sodium is low. A water diuresis results from this, bringing the sodium level up to normal. If this is not done the administration of corticosteroids may precipitate cerebral edema and convulsions. We have not seen this with any preparations other than ACTH, but it has been reported.

Infections and antibiotics

There is some disagreement about cessation of treatment during infections. Metcoff[2] believes that he has seen fewer serious reactions with cessation of therapy. Cooke, Lange, Heymann and Guild do not stop therapy and it has often been our practice to increase the dose during infections. Most authorities agree that therapy should be continued if the infecting organism can be adequately covered with an antibiotic, but many are uncertain about what to do in the case of infections which cannot be covered, particularly infections which may possibly be aggravated by corticosteroids such as varicella. The author has carried 2 patients through varicella on steroids without mishap, but this not mean that it can always be done.

Heymann[7] gives routine antistreptococcal prophylaxis in the form of Gantrisin. No one is really sure that this helps, and most prefer to treat the infection when it occurs if recognized. No controlled series has been reported on this subject.

The complicated case

The patient who develops serious hypertension or who has a precipitous rise in nonprotein nitrogen presents a special problem. Once diuresis is established, the blood pressure and nonprotein nitrogen may fall rapidly, but in cases in which diuresis is delayed, temporary cessation of treatment may be necessary. If prompt improvement in blood pressure and/or nonprotein nitrogen occurs, a compromise treatment of 1 or 2 days a week can be tried and gradually built up as tolerated. Permanent hypertension is a serious deterrent but may sometimes be controlled with drug therapy, especially hydralazine.

Collateral therapy

Chlorothiazide and other diuretics are useful in some patients but do not prevent albuminuria and renal failure. Salt poor albumin does not affect the renal lesion but may be a helpful adjunct in the severely edematous subject. Nitrogen mustards are seldom mentioned now and seem to add little to corticosteroid therapy. Guild and a few others believe that gamma globulin given once or twice a month reduces the number of infections. Others believe that infections other than coccal ones occur no more frequently than in the normal population. No one seems to have had a controlled series treated with gamma globulin.

A low sodium diet with potassium supplement may be needed when the larger doses are being administered, even with the newer preparations. This is particularly true if chlorothiazide or another saluretic agent is being employed.

Bed rest is a useful adjunct in rendering the patient free of edema initially and may be resorted to in the more severe relapses. It is more difficult to keep the urine free of albumin if the subject is ambulatory, but the improved morale and the practical value of the ambulatory state seems to us to outweigh this disadvantage. We advise against competitive sports for 6 months after the urine clears and then suggest a gradual increase in activities controlled by daily urine tests.

Spirolactone[1] failed to eliminate edema in 4 patients reported by Milton Rapoport.

Prognosis of the aggressively treated patient as compared to the patient who has received no treatment at all is difficult to ascertain since historical controls cannot safely be matched with patients being treated currently. No investigator seems willing at the present time to alternate cases and it is doubtful whether any subject or his parents would permit any patient to be used as a control regardless of the physician's wishes. Riley's data indicate that the 5 year survival rate of patients whose disease began in the pre steroid era but after the advent of antibiotic therapy is roughly 20 per cent less than the survival rate of patients who acquired the disease

in 1952 or later This suggests and most investigators agree that we are prolonging life but there are still insufficient data to say that we are changing the eventual outcome Few seem to question the fact that corticosteroids have diminished the morbidity and improved the ability of the average patient to live a more normal life than before Lange has treated his patients more intensively and consistentl than any other group has been treated and eventually a detailed analysis of his cases may be rewarding including a report on those patients discontinuing and excluded from treatment

REFERENCES

1 Riley C Proceedings of the Sixth Annual Conference on the Nephrotic Syndrome 1954 p ?60
2 Black R L and Oglesby R B Subcapsula cataracts induced by corticosteroid J A M A I 4 166 1960
3 Heimann W G and Freiberger R H A colar necrosis of the femoral and humeral head after high-dosage corticosteroid therapy New England J Med 263 672 1960
4 Riley C Proceeding of the Eleventh Annual Conference on the Nephrotic Syndrome 1960 p ?84
5 Lange K Proceeding of the Eleventh Annual Conference on the Nephrotic Syndrome 1960 p 288
6 Merrill A J The nephrotic syndrome Am Heart J 53 305 19 7
Heymann W Proceedings of the Eleventh Annual Conference on the Nephrotic Syndrome 1960 p 289
8 Luetscher J A and Mulrow P A The nephrotic syndrome Disease Month August 1956
9 Metcoff J Proceedings of the Eleventh Annual Conference on the Nephrotic Syndrome 1960 p 292
10 Cooke R Lange K Heymann W and Gould H Proceedings of the Eleventh Annual Conference on the Nephrotic Syndrome pp 292 ?93
11 Rapoport M Proceedings of the Eleventh Annual Conference on the Nephrotic Syndrome p 286
12 Riley C Proceedings of the Tenth Annual Conference on the Nephrotic Syndrome 1959 p 173

Clinical communications

Silent mitral incompetence

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The presence of an apical systolic murmur has long been recognized as a prerequisite for the diagnosis of mitral incompetence So important in fact is this physical sign that mitral incompetence is frequently diagnosed on the basis of murmur alone According to Brigden and Leatham[1] Hope (1849) was the first to relate the presence of a mitral systolic murmur to mitral regurgitation and for the rest of the nineteenth century with the exception of Potain apical systolic murmurs were regarded as organic and attributed to mitral incompetence The influence of Graham Steell and Sir James MacKenzie followed by Lewis[4] and more recently Evans led to a break with this traditional view with the result that the mitral systolic murmur was relegated to insignificance The pendulum had swung too far however Sprague and White Boone and Levine[7] Fishberg and Master were among those who felt that a mitral systolic murmur could not be regarded as innocent and insignificant and with the advent of cardiac surgery this view has been justified

Gross organic mitral incompetence is readily diagnosed by the almost invariable presence of a loud apical pansystolic murmur Greatly reduced cardiac output from uncontrolled cardiac failure or arrhythmia may soften the murmur but in the absence of such factors it is not sufficiently appreciated that gross mitral incompetence may be murmurless Thus although the interpretation of a systolic murmur at the apex may at times be debatable it is generally held that the diagnosis of mitral incompetence is very seldom tenable or even worth considering in the absence of a murmur

We report here the occurrence of silent mitral incompetence The absence of any murmur systolic or diastolic in all but one of the six cases resulted in failure to consider valvular heart disease in the differential diagnosis at the bedside However the salient clue in all was disproportionate left atrial enlargement which led to the appropriate investigations and the correct diagnosis of gross but silent mitral incompetence It seemed worth while to draw attention to this situation since mitral incompetence may well be correctable by surgical methods and the absence of murmurs may lead to the diagnosis of myocardiopathy of unknown origin

F[illegible] Ca[illegible] Cl[illegible] G[illegible] B[illegible] and C S I R Cardio-Pulmonary G[illegible] D[illegible] of Medic[illegible] University of Cape T[illegible] Cape T[illegible] South Africa
Part of the expenses for th[illegible] have been defrayed by gra[illegible] Council for Scientific and Industrial Re[illegible] and the C[illegible] of Cape Town
Rece[illegible] 1960



Fig. *1.* Appearance of the mitral valves from the left ventricle and left atrium; both chambers are hypertrophied and dilated. The valve ring is dilated and gross mitral incompetence is present. The valves are sclerosed and the chordae are thickened, fused, and shortened with fibrosis of the papillary muscles.

Case reports

Case 1. G. C., a 70-year-old white woman, was first seen in August, 1951, with a history of normal health until the occurrence of an attack of acute nocturnal dyspnea 3 months before. From that time on she noticed effort dyspnea which was progressive until she began to experience orthopnea and paroxysmal nocturnal and diurnal dyspnea. On examination she was found to be in atrial fibrillation, moderate jugular venous distention, and a 6 cm. tender hepatomegaly. Her eyes were prominent and the thyroid was nodular. Her blood pressure was 205/120 mm. Hg, the apex was left ventricular in type and displaced outward. An intermittent third heart sound was audible. *Repeated examination failed to elicit any murmurs.* With bed rest and digitalis the blood pressure soon dropped to 160/90 mm. Hg.

The electrocardiogram showed atrial fibrillation and digitalis effect. On radiologic examination generalized cardiomegaly was present, the left atrium being disproportionately affected. Valvular calcification was not detected.

Cardiac catheterization with saline manometry revealed a cardiac output of 2.5 liters per minute. Thyrotoxicosis was excluded by the low cardiac output and negative tests for hyperthyroidism available at the time. A diagnosis of *silent rheumatic valvular disease* and systemic hypertension was made.

Thereafter the patient was admitted on five occasions because of congestive cardiac failure. On her second admission in 1953 the blood pressure was 160/?0 mm. Hg and the heart had become grossly enlarged with the apex in the seventh intercostal space in the midaxillary line. A harsh systolic murmur was now audible over the whole of the front of the chest but maximal at the apex. On her next admission in 1954 a mid-diastolic apical murmur was audible and the blood pressure was 195/105 mm. Hg. On her readmission in 1955 a systolic murmur was not heard but the diastolic murmur was audible. Her terminal admission in 1956 was associated with a blood pressure of 140/75 mm. Hg. A striking triple rhythm was present with a Grade 3 systolic murmur at the apex.

At necropsy the heart weighed 482 grams and was markedly enlarged. The right atrium was dilated and was filled with postmortem clot. The coronary sinus admitted a thumb and its orifice was traversed by Chiari's network. The atrial appendage was full of organizing thrombi; the tricuspid and pulmonary valves were healthy and the right ventricle was not obviously hypertrophied. The left atrium was thin walled but enormously dilated with focal nodularities and thickening suggesting old organized mural thrombi. The mitral valve admitted three fingers readily (Fig. 1). There was no stenosis. The mitral valves were thickened and distorted. The chordae were fused, thickened, and shortened with fibrosis of the papillary muscles; the left ventricular wall measured 1.6 cm. and was hypertrophied. Congestive cardiac failure was marked with fine cirrhosis of the liver and pulmonary congestion. Microscopic examination showed hypertensive vascular changes in the kidneys and the adrenals. The changes in the papillary muscles, chordae, and mitral valves were conceded to be rheumatic in origin.

Case 2. A. D., a 33-year-old Malay male, was first seen in February, 1957. He had been quite well until 9 months previously when he began to feel short of breath on effort. At first this was slight but deterioration was progressive. In November, 1956, he had an attack of paroxysmal nocturnal dyspnea and thereafter the attacks recurred almost nightly so that he was forced to give up his work. There was no history of rheumatic fever. On examination at the Medical Outpatients Department he was found to be in cardiac failure with gross dyspnea, for which mercurials and digitalis were administered. No murmurs were audible at that time. The electrocardiogram showed left ventricular damage.

When he was examined in the Cardiac Clinic a month later the jugular venous pressure was found to be considerably elevated and hepatomegaly was still present. The pulse was normal and the blood pressure was 140/100 mm. Hg. The apex beat was in the fifth intercostal space in the anterior axillary line and was left ventricular in type. *No murmurs were audible.* Screening showed disproportionate left atrial enlargement, a large left ventricle, and hilar congestion. The cause of the heart failure was obscure but a diagnosis of silent mitral incompetence was entertained.

The patient remained under regular treatment and after 18 months was still edematous with hepatomegaly and an apical triple rhythm but no murmurs. In May, 1960, he was admitted for cardiac catheterization; the signs and symptoms were completely unchanged. The phonocardiogram showed a loud third heart sound but no murmurs (Fig. 2,*A*). By now atrial fibrillation had developed, the left ventricle had enlarged further, and marked left atrial enlargement was still present on x-ray examination (Fig. 3,*A*).

At cardiac catheterization the right atrial pressure was 11/5 mm Hg with a mean of 7 and a CV wave of 3 mm. The right pulmonary arterial wedge pressure was 42/22 mm Hg with a mean of 25, CV wave of 20 mm and a sharp Y descent (Fig. 4 A). The pulmonary arterial pressure was 55/25, the radial arterial pressure 135/75 and the left ventricular pressure 125/12 to 25 mm Hg. Simultaneous diastolic pressures from the right pulmonary arterial wedge and left ventricle showed a 2 mm diastolic gradient which was probably due to the difference in manometric levels, the pressures were 22-27 and 20-25 mm Hg respectively (Fig. 5). There was no gradient between the left ventricle and aorta. The cardiac output was 3 liters per minute and atrial fibrillation was present.

The injection of 50 of 90 per cent Hypaque into the left pulmonary artery barely outlined the pulmonary arteries and veins because of the very slow circulation. Cardiogreen injected into the left ventricle and aorta with sampling from the femoral artery showed curves of nearly normal contour. The left ventricular injection was slightly more spread out than the aortic, suggesting a large left ventricle or some mitral insufficiency. Both pulmonary arterial and superior vena caval injections produced very flat spread out curves with disproportionate prolongation of the disappearance slope, giving a CL CR ratio of 0.85 which suggested very large pulmonary and left atrial volume together with insufficiency of the mitral valve. The curve recorded after injection into the superior vena cava was not significantly different from that recorded after injection into the pulmonary artery, suggesting that the right heart volume was not unduly large and that there was no severe tricuspid or pulmonary incompetence.

The catheter findings thus indicated pulmonary venous hypertension secondary to an elevated left ventricular end-diastolic pressure with no mitral valvular gradient during diastole. The wedge contour and dye curves suggested a significant degree of mitral insufficiency. The diagnosis made was *silent mitral incompetence with atrial fibrillation presumably due to rheumatic mitral valvular disease.* Mitral incompetence secondary to cardiopathy of unknown origin could not be excluded.

Case 3. P. F., a 41-year-old white woman, was seen in September 1957. When she was 18 years old an anesthetist had first drawn her attention to a cardiac murmur. There had been no history of rheumatic fever prior or subsequent to this. She had a normal pregnancy but about 13 years before admission she had noticed palpitations for the first time. In 1952 she developed paroxysmal disturbances of rhythm and was found to have atrial fibrillation but no evidence of heart failure. Three years later she was forced to give up playing tennis because of dyspnea. This was followed by increasing symptoms which progressed to swelling of the feet and abdomen necessitating digitalization, diuretics and hospitalization.

On examination she was in gross heart failure with marked venous congestion, tricuspid incompetence and hepatomegaly. Atrial fibrillation under digitalis control was present. The apex was quiet with right ventricular activity medially and a lift over the pulmonary outflow tract. On auscultation

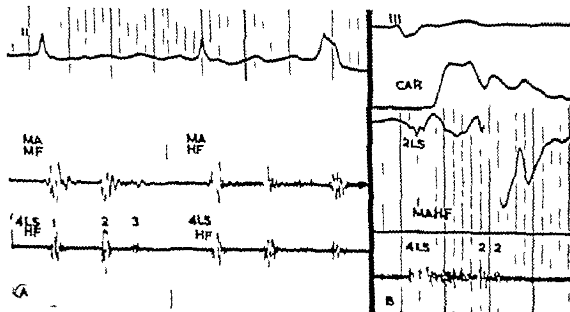
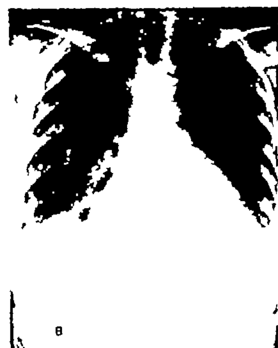


Fig. 2. Phonocardiograms at the mitral (*MA*) and fourth left intercostal space (*4LS*), high frequency (*HF*) and medium frequency (*MF*) from Case 2 (*A*) and Case 3 (*B*). Atrial fibrillation is present in both. In Case 2(*A*) third heart sound is recorded but there are no murmurs. (Base line artefact is present.) In Case 3 (*B*) a pansystolic murmur is present at the fourth left intercostal space with wide splitting of the second sound, but no murmur is shown at the mitral area. The external carotid arterial tracing (*CAR*) and apex cardiogram from the second left intercostal space (*2LS*) are synchronously recorded.





F 3 Anteroposterior and left obliq e iews from Case 2 (A) and Case 3 (B) D proportionate left atrial enlargement present both

there w despread triple hythm audible t all area After sh exercised the third sound became m rmur l ke nd w ft tolic murmur ppeared Phonocardiography (Fig 2 B howed tricu pid y lic murmur and plitt ng f the second sound but no mitral y t le murmur The lectrocardiogram howed combined heart ram with digitalis effect On ray examination moderate cardiomegal w present w th d proporti nat left atrial enlargement (Fig 3 B)

At cardiac catheterization the mean right trial pres ure a 22 mm Hg with a CV wav of 13 22 mm indicatn f tricu pid incompetence The right pulmonary arterial ed tracing showed a

CV wave of 15 mm with a sharp Y descent and a mean of 35 mm Hg (Fig 4 B) The pulmonary arterial pressure was 50/30 the right ventricular pressure 51/6-17 and the femoral arterial pressure 100-1 0/77 mm Hg Atrial fibrillation was present The cardiac output was 3 4 liters per minute and the tricuspid valve was normally situated The catheter findings thus indicated pulmonary venous hypertension with significant mitral incompetence and moderate pulmonary arterial hypertension with significant tricuspid incompetence Ebstein anomaly which was one [illegible] suggestion was excluded

The diagnosis at the time of the patient discharge was silent mitral incompetence presumably due to rheumatic mitral [illegible] disease with atrial fibrillation Necropsy was not performed when she died some months later

Case 4 N S a 53 year-old white male physician was first seen in June 1959 at the age of 53 years with the following history As medical student 34 years before he first became aware of premature systoles He was seen by Sir Maurice Cassidy at that time and was told that he had no heart disease Seven years later he developed asthma from which he suffered for many years finally developing several attacks of status asthmaticus associated with chronic emphysema For the past 10 years since he has been in Cape Town he has been free of actual asthmatic attacks although he has suffered from chronic wheezing and dyspnoea In 1943 he woke up one night with an attack of paroxysmal tachycardia and on examination shortly afterward was found to have developed atrial fibrillation In June 1951 after an unsuccessful attempt at quinidine conversion he was digitalized and has been kept on maintenance dose ever since The electrocardiogram showed atrial fibrillation right axis deviation ventricular ectopic beats left ventricular hypertrophy and digitalis effect X ray examination showed moderate cardiac enlargement with mitral contour and disproportionate left atrial enlargement [illegible] In June 1958 he was readmitted to the hospital for noncardiac reasons and again there were no abnormal auscultatory findings In September 1959 he had an attack of pyrexia followed by the signs and symptoms of congestive cardiac failure

On examination he was in right heart failure The jugular venous pressure was raised to 20 cm with the CV wave of tricuspid incompetence and the liver was distended five fingerbreadths Atrial fibrillation was present with numerous ectopic beats and the blood pressure was 115/ 0 mm Hg The apex was in the sixth intercostal space 1 inch beyond the anterior axillary line and was left ventricular thrusting in character The first heart sound was normal in intensity and [illegible] occasion [illegible] Grade 1 2 pansystolic murmur was audible at the mitral and tricuspid areas

The electrocardiogram showed atrial fibrillation ventricular ectopic beats combined heart strain and digitalis effect The X-ray film (Fig 6 1) showed very striking cardiomegaly with almost aneurysmal dilatation of the left atrium Calcification of the mitral valves was not seen Comparison with previous plates taken in 1951 showed quite definite increase in the size of the heart

Recent examination has shown improvement in symptoms but no change in the heart size A very soft (Grade 1) short murmur was present at the mitral and tricuspid areas and phonocardiography showed coupling due to ventricular premature systoles but no mitral systolic murmur (Fig 7 1)

Case 5 C W 35 year-old Coloured woman first seen on Aug 30 1957 She had been quite well until 2 weeks before when she developed an influenza-like illness with sore throat, body pains pyrexia and sweating She stayed in bed for 2 days On the third day she returned to work but did not feel well On the fourth day she suddenly noticed swelling of the abdomen and pain in the chest which was worse when she coughed or breathed deeply A day later her legs and face began to swell From then on progressive dyspnoea developed and paroxysmal nocturnal dyspnoea ensued Herpes of the abdominal wall anorexia and vomiting were the other symptoms

On admission to the hospital she was obese orthopnoeic and in congestive failure with edema raised venous pressure and hepatomegaly The

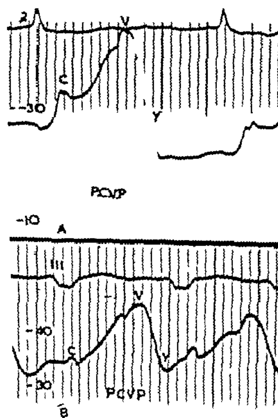


Fig 4 Right pulmonary arterial wedge pressure records from Case 2 (A) and Case 3 (B) The markedly elevated pressure is shown in both with dominant CV wave of mitral incompetence and sharp Y descent Atrial fibrillation is present in both patients

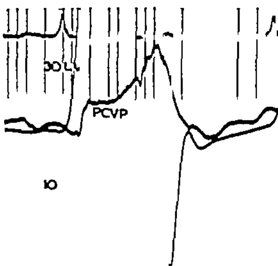


Fig 5 Synchronously recorded right pulmonary arterial wedge and left entricular pressures showing the high end-diastolic pressure in the left ventricle the absence of a diastolic gradient and the presence of a large CV wa e of mitral incompetence

blood pres ure was 140/80 mm Hg N *murmurs ere aud ble* but triple rhythm was present The electrocardiogram showed left trial enlarge ment and left entricular damage X ray examina tion bowed cardiomegaly with prominent pulmonary arteries.

When she was seen in the Cardiac Clinic week later the blood pressure was 130/90 mm Hg and he was no longer in cardiac failure The fir t sound was palpable and accentuated and the second sound was pl t with accentuation of the pulmonary component (Fig 7 B) Screening bowed large pulmonary arteries and disproportionate left trial enlargement

She as examined on several occasions thereafter and at no time were any murmurs noted The electrocardiogram remained bnormal with per tence of left trial hypertrophy and left entricular damage A diagnosis of acut myocarditis as ma le with acute heart f ilure and silent mitral incom petence

After discharge he remained well without treat ment and apart from dyspnea on moderate effort he w mptom free Early in Augu t 1960 however her symptoms returned and she was admitted with nkle edema and abdominal welling The phy cal signs were the same as on her f t admission with edema jugular enou distention hepatomegal pleural effu ion and proteinuria Cardiomegaly was ain noted clinically and radi ologically w th disproportionate left atrial enlarge ment (Fig 6 B) The heart sound were unchanged and there were no murmurs

The diagnosis ma le wa ilent mitral incompe tence in a sociation ith myocardial failure of unknown origin.

Cas 6 J S 35 year-old unemployed Coloured man wa first seen in July 1958 Three years before he had developed hemoptysis for which he had ttended a tuberculosis clinic and despite repeatedly negative sputa had been treated with streptomycin and later noniazid X ray films were always negativ for tuberculosis About once a month he was subject to attacks of paroxysmal nocturnal dy pnea which lasted half an hour t time but during the day his effort tolerance was reasonably sati factory Frequently repeated hemoptysis was striking symptom

On examination of the patient the jugula enous pressure was normal and there was no evidence of heart failure The pulse was normal and the blood pressure was 130/90 mm Hg The apex was left entricular in type in the normal site a Grade 1 2 first heart sound was pres t with a long Grade 2/4 diastolic murmur and suspended presystolic murmur associated w th first-degree block. *No murmur was audibl in systole* on caref l ausculta tion Nor was there an opening snap The signs suggested fibrotic or calcified mitral alves but calcium could not be seen on screening The left trium was enlarged radiologically and electro cardiographically Operation was deferred

The patient returned to work but soon developed acute nocturnal dyspnea w th pulmonary edema for which he was admitted to a tuberculosis ho pital where he had several episodes of hemoptysis and was kept in bed for 5 weeks before transfer On examination he was now found to ha developed trial fibrillation and a ery soft Grade 1/6 pical systolic murmur The other signs were virtually unchanged An operation was advised fter digitali zation and diuretic therapy At operation the pulmonary artery was found to be sl ghtly larger than the aorta with a pressure of 35/15 mm Hg The pressure in the left atrium was at least 25 mm Hg w th large CV wa es of mitral incompetence I tracardiac palpation of the mitral valve revealed a systolic thrill and systolic jet with calcification around the margin of the al es The orifice of the alve was at least 3 5 cm in diameter and operation on the mitral alv was not ttempted The post operative course was sati factory the arrhythmia was temporarily corrected with quinidine but soon reverted to trial fibrillation For the first 2 post operative months he felt much improved Re examination of him as an outpatient showed a Grade 2/6 mitral systolic murmur and a Grade 2/4 mid-diastolic murmur t the pex H failed to reattend until year later when he reported with return of symptoms For 3 months he had been ha ing recurrent attacks of paroxysmal nocturnal dy pnea and a week prior to admi sion he had experienced frequent palpitations Examination re ealed the hythm disturbance to be that of flutter with arying block there was actually no *systolic* murmur audible t the pex H was digitalized and discharged after 4 days Five months later he returned with paroxy mal nocturnal dyspnea hemop tysis and progres i dyspnea He now had trial fibrillation and on auscultation a Grade 1 2 y tolic murmur was audible at the apex. Treatment was continued and he was not seen for a year when he reported w th recurrence of ymptoms On this occa ion a Grade 2 3 mitral systolic murmur had become clearly udible A year later his con dition was unchanged

Discussion

Six cases of severe mitral incompetence with no murmur of mitral incompetence have been presented. In the first case cardiac catheterization was performed to exclude thyrotoxicosis as a cause of obscure heart failure with atrial fibrillation and a nodular goiter. The disproportionate enlargement of the left atrium radiologically suggested rheumatic valvular disease and this was proved at necropsy 5 years later when gross rheumatic valvular disease with pure mitral incompetence was demonstrated. The absence of murmurs could not be entirely attributed to the low cardiac output and severe heart failure since the condition remained silent even when the patient had improved and was well enough for discharge. Moreover as her condition deteriorated and her blood







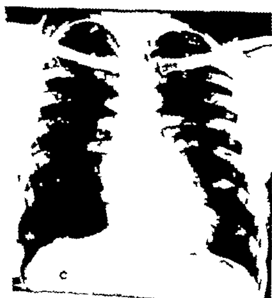


Fig 4 The anteroposterior and right oblique diagrams in Case 4 (A) show considerable left atrial enlargement does the right oblique view in Case 5(B). In Case 6(C) the anteroposterior view shows virtually normal cardiac silhouette

The degree of incompetence was gross in every case and it may well be that severe mitral incompetence like tricuspid incompetence [3] can occasionally be silent The degree of incompetence is probably a more important factor than the presence of cardiac failure atrial fibrillation or any myocardial (muscular) factor

Summary

1 A systolic murmur usually described as loud and holosystolic is the conventional hallmark of mitral incompetence

2 Six cases of silent mitral incompetence are described in which murmurs were absent at the apex despite the presence of gross mitral regurgitation In three cases despite frequent examination over long periods no murmurs could be heard or recorded by phonocardiography at any time In the other three soft mitral systolic murmurs were sometimes present and sometimes absent

3 Heart failure and atrial fibrillation did not appear to be responsible for these findings

4 In all six patients radiologic examination showed disproportionate enlargement of the left atrium and provided the clue to the correct diagnosis

5 Rheumatic mitral valvular disease was proved at necropsy in one and at operation in another Cardiac catheterization established the diagnosis but not the etiology in two

6 Gross mitral incompetence can occur in the absence of any audible systolic murmur

We wish to thank members of the Staff of Groote Schuur Hospital for referring cases for investigation and the Superintendent Dr J Burger for permission to publish We acknowledge the great help received from our Chief Technician Mr L W Filler and his associates Mr R de Meneau and Mrs S Joseph in the cases catheterized

REFERENCES

1 Brigden W and Leatham A Mitral incompetence Brit Heart J 15 55 1953
2 Steell G Textbook on diseases of the heart Manchester England 1906 Manchester University Press
3 Mackenzie J Principles of diagnosis and treatment of heart affections London 1916 Oxford Medical Publications
4 Lewis T Diseases of the heart London 1933 The Macmillan Company
5 Evans W Cardiology London 1948 Butterworth Ltd
6 Sprague H B and White P D A comparative study of rheumatic mitral regurgitation and mitral stenosis Am Heart J 1 629 1926
7 Boone J A and Levine S A The prognosis in potential rheumatic heart disease and rheumatic mitral insufficiency Am J M Sc 195 764 1938
8 Fahlberg A M Heart failure ed 2 Philadelphia Lea & Febiger
9 Master A M Apical systolic murmur Arch Int Med 81 518 1948
10 Freeman A R and Levine S A The clinical significance of the systolic murmur Ann Int Med 6 1371 1933
11 Wood P An appreciation of mitral stenosis Parts 1 and 2 Brit M J 1 1051 and 1113 1954
12 Ross J Braunwald E and Morrow A G Clinical and haemodynamic observations in pure mitral insufficiency Am J Cardiol 2 11 1958
13 Venner A and Holling H E Comparison of operation and clinical findings in mitral stenosis and incompetence Brit Heart J 15 205 1953
14 Van der Veer J B Mitral insufficiency Historical and clinical aspects Am J Cardiol 2 5 1958
15 Bleifer S Dack S and Grishman A The auscultatory and phonocardiographic findings in mitral regurgitation Am J Cardiol 5 836 1960
16 Lim C K Araujo C Testelli M P and Lasseda A A Intracardiac phonocardiography in mitral and aortic valve lesions Am J Cardiol 1 379 1958
17 Ellis L B Abelmann W H and Harken D F Selection of patients for mitral and aortic valvuloplasty Circulation 15 924 1957
18 Burchell H B and Edwards J E Rheumatic mitral insufficiency Circulation 7 747 1953
19 Logan A and Turner R The diagnosis of mitral incompetence accompanying mitral stenosis Review of eleven cases treated surgically Lancet 2 593 1952
20 Logan A and Turner R Mitral stenosis Diagnosis and treatment Lancet 1 1006 and 1057 1953
21 Dexter L McDonald L Rabinowitz M Saxton G A and Haynes F W Medical aspects of patients undergoing surgery for mitral stenosis Circulation 9 758 1954
22 Schlider D I and Proctor Harvey W Confusion of tricuspid incompetence with mitral insufficiency—a pitfall in the selection of patients for mitral surgery Am Heart J 54 352 1957
23 Reeves S and Carral R The diagnosis of tricuspid valve disease Am Heart J 34 114 1947
24 Muller O and Shillingford J Tricuspid incompetence Brit Heart J 16 194 1954

The genesis of bidirectional tachycardias

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Several mechanisms for the production of bidirectional tachycardias have been proposed.[22] This is not surprising in view of the uncertain origin of arrhythmias which have a rapid rate with prolonged and bizarre QRS complexes.[1] As in all cases of complex disorders of rhythm, a complete knowledge of cardiac physiology is required. But in addition, the technician should be taught to obtain long strips of the electrocardiogram, mainly in one lead, so that the greatest number of pathologic mechanisms can be recorded, as can be seen in Figs. 1-7 of this communication.

Because of the complexities seen in short (conventional) tracings, certain authors have advanced the theory that bidirectional tachycardia probably represents a heterogeneous group of cases which have similar electrocardiographic configuration.[1] For example, some workers have postulated the existence of two pacemakers, either one supraventricular and one ventricular, or two ventricular ones.[2] Moreover, others believe that the paroxysm originates in one single focus before[1 ...] or after the bifurcation.[22] Precisely, this communication establishes that not one

Table 1

Case	Age (yr.)	Etiology	Heart failure	Digitalis	Atrial rhythm during paroxysm	Esophageal leads	Alternation in direction in Lead I	Ventricular rate
1	63	AHD	Yes	++++	A F	Yes	No	157
2	68	AHD	Yes	++++	A F	Yes	No	158
3	0	AHD	Yes	++++	A F	Yes	No	150
4	65	AHD	Yes	++++	S R	Yes	No	167
5	88	AHD	Yes	++++	S R	Yes	No	150-172
6	71	AHD	Yes	++++	A T	Yes	No	115
7	75	AHD	Yes	++++	A T	Yes	No	168
8	69	AHD	Yes	++++	A T	Yes	No	176-188
9	71	EM	No	+	A-V T	No	No	167-180
10	63	AHD	Yes	++	A-V T	Yes	No	1[illegible]0
11	65	AHD	Yes	++++	A F	No	Yes	16[illegible]
12	84	AHD	Yes	++++	A F	Yes	No	16[illegible]
13	9	DM	No	No		No	No	130
14	9	NH	No	No	A T	Yes	No	188-275

AHD, Arteriosclerotic heart disease; EM, Endocardial myocarditis; DM, Diphtheritic myocarditis; NH, Normal heart; A.F., Atrial fibrillation; S.R., Sinus rhythm; A.T., Atrial tachycardia; A-V T, Atrioventricular nodal tachycardia.

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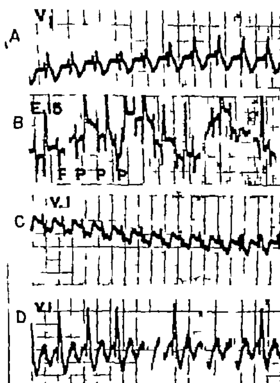


Fig 1 Bidirectional tachycardia of atrial origin These tracings were obtained from 9 year-old hematic girl with bouts of repetitive paroxysmal tachycardia but no heart disease A pra entricular tachycardia (rate 188 per min) with aberration bowing different degrees of right sided intraventricular conduction defect can be seen in A The esophageal lead (B) clearly establishes the atrial origin of the paroxysm 1 C different degrees of aberration are seen again Finally in D when the rate speeded up t 2 5 per min a curious form of alternation is present an rsR complex of lower duration and smaller height alternates with one of greater duration and height This record is interpreted as an example of atrial tachycardia with bidirectional complexes due to alternating aberrant ventricular conduction The warming up of the ectopic center is attributed to a mechanism similar to the rhythm of development.[18]

but several mechanisms are involved in the genesis of what has been called bidirectional tachycardia from a simple morphologic configuration Prognosis and treatment will not be considered here

Material and methods

Our material consists of 14 records showing bidirectional tachycardias (other tracings from these patients have been included in previous reports[12 15]) All subjects except 3 (Table I) had arteriosclerotic heart disease and varying degrees of congestive failure The detailed clinical data are presented in Table I It is to be noted that esophageal leads were obtained simultaneously with a conventional lead whenever the coexisting supraventricular rhythm *during* the paroxysm could not be ascertained with accuracy The term bidirectional tachycardia as used in this report assumes the existence of a rapid ectopic rhythm with a rate ranging in 80 per cent of the cases from *150* to *188* (Table I) and rhythmical alternation of QRS complexes (either prolonged or normal) although such ventricular complexes are not necessarily inscribed in opposite direction in each lead Generally the rhythm is regular but occasionally the rate as well as the interval between the complexes of different morphologies may vary more than 0 04 second

Results

Of the 14 cases studied there were 5 in which the corresponding records showed certain characteristics which could be of help in clarifying the genesis of bidirectional tachycardias These cases are presented in Figs 1 7 and the corresponding electrocardiograms are fully described in the respective legends Table I shows the basic features

Comment

Many theories have been proposed to explain the genesis of bidirectional tachycardias [1 14] Some have received widespread attention[1 4 11] others such as the double circus movement of White and Palmer [13] have been practically forgotten One of the earliest assumptions favored the ventricular origin of the paroxysm [7] This was due to the observation that many cases showed frequent ventricular extrasystoles prior to or after the tachycardia Thus it was considered that the two morphologies corresponded to two foci of impulse formation that is one in each ventricle

Such a theory has been challenged in later years since the work of Zimdahl and Kramer [8] who showed that one of the two complexes in their case could be abolished by carotid sinus pressure and thus postulated that two active centers were present—one ventricular and one supraventricular Similarly other authors

have since reported instances of disappearance of the arrhythmia by this or allied vagomimetic procedures.[4,11,14] However, the unquestionable ventricular origin of bidirectional tachycardia was established in Figs. 4 and 5 by the presence of fusion beats; the alternating complexes were explained on the basis of irregular intraventricular propagation. Furthermore, this case is a clear example of the abolishment of a ventricular tachycardia by carotid sinus pressure, so that the effectiveness of this procedure cannot be related necessarily to the existence of a supraventricular tachycardia. It should be emphasized that Scherf has reported the slowing of ventricular parasystole by carotid pressure indicating the response of ventricular rhythms to vagus stimulation. Similarly, the transition of bidirectional to unidirectional complexes without changes in rate also rules out the diagnosis of double ventricular paroxysmal tachycardia. Evidently, this possibility is to be considered extremely rare because no instance of this arrhythmia was found in a recent review of 15 cases of simultaneous tachycardias.

Occasionally it has been considered that the disappearance of one type of beat with halving of the ventricular rate after

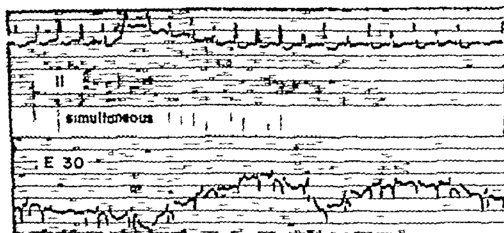


Fig. Bidirectional tachycardia originating in a supraventricular center, probably the A-V node. The tracings start with regular tachycardia (rate 16 per min.) and QRS duration of 0.06 sec. Note that it is dissociated from an independent sinus rhythm (rate 103 per min.) and that the P waves have predominantly negative deflection in the esophageal lead (E 30). Alternation in the height of ventricular complexes appears toward the middle of the tracing and is best seen in Lead II. The records continue with that of Fig. 3.

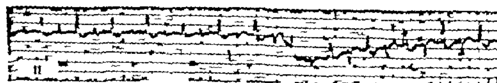


Fig. 3. Bidirectional tachycardia originating in supraventricular center, probably in the A-V node. This tracing is continuous with that of Fig. 2, and shows, besides an alternation in the height of ventricular complexes, progressive alternation in direction of QRS and T. The characteristic bidirectional tachycardia appears toward the end of the record. In Figs. 2 and 3 the smooth, regular and constant rate and the gradual evolution from unidirectional to bidirectional alternation, in association with only moderate changes in ventricular duration (which is within normal limits, 0.08 sec.) and rate, lend support to the assumption of supraventricular tachycardia with varying deviation of intraventricular propagation of rapid impulses in alternate cycles. The presence of independent sinus rhythm is against the existence of rapid atrial arrhythmia, and favors the diagnosis of A-V nodal tachycardia with aberrant intraventricular conduction. Similar QRS complexes of lesser duration (0.06 sec.) were seen in this patient after the return of normal basic rhythm.

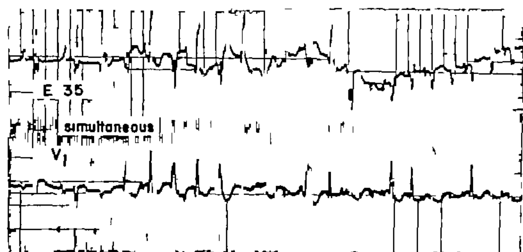


Fig. 4. Bidirectional tachycardia originating in one ventricular cente. This tracing starts ith tw normally conducted sinus beats (rat 91 per m) which precede run of bidirectional en tricula tachy ardia (rat 150 per min). The most promine t f nd ng in this record is the presence of lternation direction of QRS complexes (t duration I ng 0.11 ec) n the esophageal lead here the simult neou ly obt ned I c d V show altern tion morphology and height only. Sinus act ity persi t t t usual speed y t d sociated evidently from the entricular omplexes. A curiou phenomenon is seen tow rd the end of the tracing as the entricula rate ncreas t 172 pe min altern tion disappears completely (last thre complexes) but w th a d crease in QRS du tion t 0.09 sec. On the basis of such findings it can well be ssumed that the paroxysm arose in one center occ sionally w th and ometimes w thout e tricular altern tion. However from an inspection f this tracing the exact origi of the tachycardia (whether A V nod l or entric lar) could not be ertained.

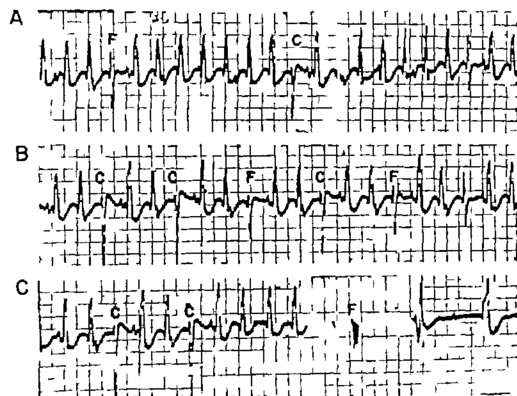


Fig. 5. ECG from same patient in Fig. 4. *(For legend see pposite page.)*

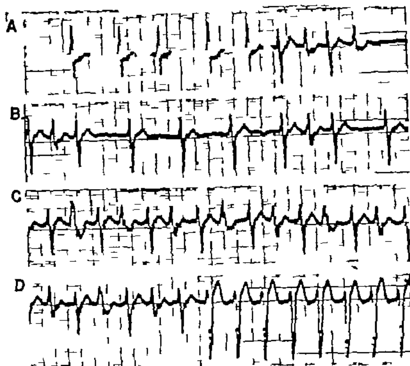


Fig 6 Bidirectional tachycardia originating one center probabl en tricular (Lead II) *A* how trial fibrillation and normal entricular rate interrupted by short run of bidirectional tachycardia (last four beats) ts rate ranging between 150 and 156 per sec *B* starts with the same tachycardia but now after the first three complexes t can be appreciated how paradoxically the smaller complexes anish and the larger QRS complexes persist t rate of 7 per min which is exactly half of the tachycardia previously present This phenomenon can well be explained by the presence of an intermittent 2 1 exit block from the ectopic center and is corroborated by the finding of another complex occurring midw y between the seventh and eighth QRS complexes The classic picture of bidirectional tachycardia ca be observed throughout *C* and the beginning of *D* Toward the middle of the latter tracing another puzzling alteration observed the alternating beat abruptly change in shape so that other beats of third morphology ppear the rat being exactly the same as that of the bidirectional tachycardia (150 per min) This unu ual arrhythmia as a whole can be interpreted as entricular tachycardia arising in one center probably entricular The arious morphologies of the QRS complexes are due to arying and irregular intra entricular propagation \ similar arrhythmia was previously reported

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Fig 5 Electrocardiograms obtained from the same patient as was Fig 4 and demonstrating the entricular origin of the tachycardia (Lead V) *A* and *B* recorded a few minutes after the preceding Fig 4 show the same tachycardia but now it is terrupted by entricular captures (*C*) and fusion beat (*F*) which show that the entricles are activ ted partly by the oncoming atrial stimulus and partly by the stimulus originating in the ectopic center Such phenomenon convincingly proves the entricular origin of the parox) m Finally *C* record the end of the tachycardia after carotid pressure was pplied Posterior to such agal stimulation fu ion beat appears followed by tw idioventricular beats resembling those seen previously This strip emphasizes that entricular tachycardia can be stopped by carotid sinus pressure Thus the disappearance of an ectopic rapid rhythm by carotid sinus pres ure does not necessarily indicate the entricular origin of the arrhythmia as has been previously assumed A milar effect on the rate of entricular parasystole was reported by Scherf[1]



Fig 7 Bidirectional tachycardia arising below the A V node *A* shows a A V nodal tachycardia (rate 125 per min) and posterior stimulation of the atria which was considered t originate the lower regions of the A V node *B* starts with two A V beats followed by an extrasystole arising ery late in the R R cycle It is followed by another nodal beat which in turn precedes a run of bidirectional tachycardia The ectopic paroxysm discharges the A V center so that a simultaneous tachycardia does not exist Since the pre exist ng rhythm had ts origin in the lower portions of the node the second (ectopic) center must be located below this region N conclusion ca be definitely drawn as t whether we were dealing with one or tw centers either before or after the bifurcation of the common bundle

vagal stimulation proves the double origin of the paroxysm[1] Yet Fig 6 as well as Fig 13 of the article by Castellanos and associates[14] show that 2 1 exit block from a single ectopic center accounts for such a phenomenon Evidence of a unifocal center is present in Figs 1 through 6

Undoubtedly bidirectional tachycardias can be of supraventricular origin a theory postulated originally by Scherf and Kisch and convincingly proved by these authors in cases of atrial tachycardias [10] and by Pick and Langendorf in instances of A V nodal tachycardias[1]

Fig 1 is an example of atrial tachycardia with aberrant ventricular conduction In some instances this functional intraventricular right sided block shows persistent alternation so that the typical image of bidirectional tachycardia is seen in Lead V_1

In Figs 2 and 3 the slow change from unidirectional to bidirectional alternation associated with only slight changes in QRS complexes of normal duration (0 08 second) supports the assumption of a supraventricular arrhythmia showing intermittent intraventricular aberration[11] Obviously it could not arise in the atria for these anatomic structures are activated by the sinus node as seen in the esophageal lead

Such findings coupled with the fact that after the disappearance of the tachycardia the morphology of the QRS complex was similar to those in Fig 2 lend support to the hypothesis which interprets the paroxysm as A V nodal in origin One main characteristic of bidirectional tachycardias was the finding of alternation in morphology but not in direction in Lead V (Table I) The opposite finding was usually but not always seen in Lead II and at several esophageal levels Nevertheless Case 11 (Table I) and Fig 9 of Pick and Langendorf's paper[11] show alternation in both parameters in Leads V_1 and V_{1R} Yet positive complexes in Lead V when present would disprove the idea of a septal center equidistant to the two bundle branches with alternating impairment of impulse propagation to the two bundle branches[13] On the other hand alternating complexes in right precordial leads are explained on the basis of functional right bundle branch block in instances of supraventricular tachycardias[12,13] (either atrial or A V nodal) and on the basis of alternating irregular intraventricular propagation if the arrhythmia is ventricular[14]

Paroxysmal tachycardia of the bidirectional type as considered in this report

is usually but not invariably produced by digitalis intoxication Table I presents evidence of 3 cases in which the main etiological factor was considered to be respectively encephalomyocarditis (Case 9) diphtheritic myocarditis (Case 13) and repetitive paroxysmal tachycardia with a normal heart (Case 14)

It should be emphasized that excessive digitalization was not the cause in 2 patients In one the tachycardia appeared after small and proportional amounts of strophanthidin acetylstrophanthidin ouabain and digoxin (Case 9) previously reported in Figs 8 9 and 10 of the paper of Castellanos and associates [14]

Summary

Bidirectional tachycardia is a descriptive term indicating a tachycardia with alternation in morphology and (or) direction of QRS complexes A review of 5 cases was made from which it could be concluded that the paroxysm originates in a single pacemaker either in the atria in the A V node or in the ventricles

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REFERENCES

1 Weinstein W J and Jick S Bidirectional tachycardia Am J Cardiol 3 343 1959
2 Zimdahl W T and Kramer L I On the mechanism of paroxysmal tachycardia with rhythmic alternation in the direction of ventricular complexes Am Heart J 33 18 1947
3 Zimdahl W T and Townsend C T Bidirectional ventricular tachycardia due to digitalis poisoning Am Heart J 4 304 1954
4 Heilman E and Lind A Bidirectional tachycardia Am Heart J 51 140 1956
Velazquez J and Kiber G A Alternating bidirectional tachycardia Am Heart J 54 440 1957
6 Luten D Clinical studies of digitalis III Advanced toxic rhythms Arch Int Med 35 57 1925
7 Felberbaum D Paroxysmal ventricular tachycardia Report of case of unusual type Am J M Sc 166 11 1923
8 Schwensen C Ventricular tachycardia as the result of the administration of digitalis Heart 9 199 1922
9 Scherf D and Kisch B Ventricular tachycardias with variform ventricular complexes Bull New York M Coll 2 73 1939
10 Scherf D and Schott A Extrasystoles and allied arrhythmias New York 1953 Grune & Stratton Inc
11 Pick A and Langendorf R Differentiation of supraventricular and ventricular tachycardias Prog Cardiovas Dis 2 391 1960
12 Katz L N and Pick A Clinical electrocardiography Part I The arrhythmias Philadelphia 1953 Lea & Febiger Fig 15
13 Calvino J M Azan L and Castellanos A J Valor de las derivaciones esofagicas en las arritmias complejas Rev cubana cardiol 16 293 19
14 Castellanos A J Azan L and Calvino J M Simultaneous tachycardias Am Heart J 59 358 1960
15 Palmer R and White P D Paroxysmal ventricular tachycardia with rhythmic alternation in the direction of the ventricular complexes of the electrocardiogram Am Heart J 3 454 1928
16 Bellet S Clinical disorders of the heart beat Philadelphia 1953 Lea & Febiger
17 Gobley M Ladopulos C P Roth F H and Scherf D Changes of ventricular impulse formation during carotid pressure in man Circulation 10 735 1954
18 Scherf D Schott A Reid E C and Chamsai D G Intermittent parasystole Cardiologia 30 217 1957
19 Castellanos A Calvino J M Azan L and Castellanos A J Supraventricular tachycardia imitating ventricular paroxysmal tachycardia in infancy J Pediat 1 330 1959
20 Gaskell W H On the innervation of the heart with special reference to the heart of the tortoise J Physiol 4 43 1833
21 Lewis T and Levy R Heart irregularities resulting from the inhalation of low percentages of chloroform vapour and their relation to ventricular fibrillation Heart 3 99 1911 12
22 Reid W D Ventricular ectopic tachycardia complicating digitalis therapy Arch Int Med 33 23 1924

The central circulating blood volume in normal subjects and patients with mitral stenosis

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Measurement of the central circulating blood volume by the Stewart-Hamilton method has become routine in most hemodynamic studies in which cardiac output is determined by arterial dilution techniques. Although the simplicity of calculating this volume has resulted in the accumulation of a plethora of data, the physiologic significance of such determinations is obscure. A major limitation to physiologic meaningfulness is related to the time boundaries of such measurements of volume and to errors inherent in the use of peripheral arterial sampling sites. The use of the central circulating blood volume as an estimate of pulmonary blood volume requires the closest approximation possible to the time boundaries of the lung, excluding the peripheral venous and arterial systems. Although such conditions can be most closely approximated by injection into the pulmonary artery and sampling from the left heart or aortic root, the practical limitations of these methods for general clinical use are apparent. The use of dilution curves recorded over the precordium for the determination of central circulating blood volume was introduced by Shipley[3] and further elaborated by Lammerant[4] as a method whose time boundaries exclude systemic arteries and veins and which obviates catheterization procedures.

The intent of our study was to measure the central circulating blood volume by using the time boundary advantage of the precordial dilution technique both in normal subjects and in patients with mitral stenosis. Since previous studies of this volume using peripheral sampling sites in patients with mitral stenosis have shown no measurable increase over normal,[1,2] the possibility of unmasking an increment in pulmonary blood volume was offered by the use of more meaningful time boundaries. A collateral objective was the measurement of the central circulating volume after exercise by a method uninfluenced by variations in flow at systemic arterial sampling sites. Although Lammerant[4] has used the precordial method extensively in both normal subjects and patients with mitral stenosis, exercise study of the central blood volume by this method in the latter group has not been made.

Method

The experimental groups consisted of 25 subjects without heart or lung disease and 14 patients with mitral stenosis. Mitral stenosis in the latter group was predominant and pure in so far as could be documented by left atrial catheterization or subsequent mitral commissurotomy; none of the patients were in overt right heart failure at the time of the study, but the

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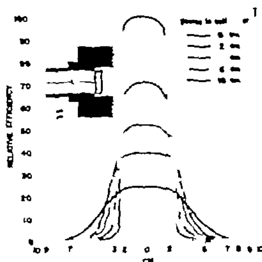


Fig. 1 The geometric characteristics of the collimator used in the study. Lead thickness of distal end of the collimator is 1 cm.

majority had clinical evidence of pulmonary hyperemia. All subjects were studied in the postabsorptive state without sedation. Eight of the normal subjects and a similar number of patients with mitral stenosis were studied before and immediately after the completion of the standard Master two step exercise tolerance test.

The determination was made with the patient comfortably seated in a special chair with adjustable arms.[9] Injections of 10 to 100 μc of I^{131} human serum albumin were made into a median basilic vein of the elevated right arm via an indwelling No. 18 Cournand needle; the isotope was contained in a volume of 2 to 3 ml. and was followed by a 10 ml. saline flush. Those subjects who were exercised were immediately reseated at the completion of the tolerance test, and the injection of isotope was made within 30 seconds of completion of the stress. All of the patients with mitral stenosis noted dyspnea at the completion of the exercise, and 2 were unable to complete the test.

The precordially placed detection device consisted of a 1½ inch sodium iodide scintillation crystal with attached photomultiplier tube mounted in series with this device was a decimal scaler counting rate computer and a pen writing Esterline Angus recording meter. The scintillation counter was shielded by a collimator, the geometric relationships of which were previously determined by a phantom radioactive source (Fig. 1). Since double peaked curves were necessary to calculate mean circulation time between right and left heart, optimal counter placement for this type of tracing has been determined by previous studies in this laboratory.[9] In the determinations of the present study, small (5 to 10 μc) preliminary injections of the isotope were made in order to verify an optimum counter position for double peaked curves. The best precordial site for securing such curves with our collimator has been along the left sternal border over the fifth or sixth ribs (Fig. 2).

Representative dilution curves recorded on semilogarithmic chart paper after the intravenous injection of 20 μc of I^{131} serum albumin in a normal subject and in a patient with mitral stenosis are shown in Fig. 3. Not all curves showed as discrete double peaks as in this illustration; such curves were discarded and only those tracings in which clear-cut exponential disappearance was apparent or could be reconstructed were used in this study. From these double peaked curves, cardiac output and mean circulation time between right and left heart were calculated for measurement of central circulating blood volume using the Stewart Hamilton equa-

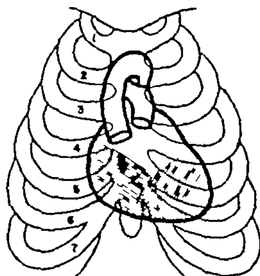


Fig. 2. Schematic projection of heart on chest wall. Cross hatched area along the left sternal border indicates optimal site for double-peaked curves. Other shaded areas give predominant right or left curves.

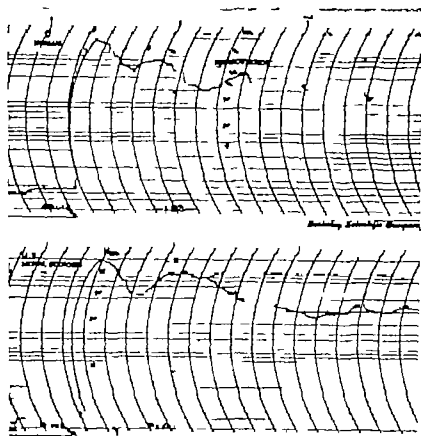


Fig 3 Representative dilution curves as recorded directly on logarithmic paper Paper speed 12 inches per minute *Above* Normal subject *Below* Patient with mitral stenosis

tion *Central Blood Volume (ml) = Cardiac Output (ml/sec) × Mean Transit Time (sec)* The mathematical methods used for curve analysis and calculation of these parameters were similar to those of Shipley[8] and Hammerint More recently we have devised a mathematical method of biphasic dilution curve analysis that has simplified the calculation of cardiac output and mean transit time [9] The time boundaries of this calculated blood space include half of the right heart the lungs and half of the left heart Total blood volume was determined by the in vitro counting of a sample of whole blood obtained from the patient 10 minutes after the completion of each determination of output

Results

Resting Table I summarizes the mean values for central circulating blood volume and the associated parameters for its de

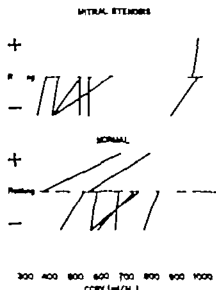


Fig 4 Directional change of central blood volume from resting, after standard exercise in normal subject and patient with mitral stenosis

termination in the normal subjects and in the patients with mitral stenosis. Although the mean value for the central volume expressed either as a function of body surface area or as a percentage of total blood volume is greater in the patients with mitral stenosis (678 ml./M.², 27 per cent of total blood volume) than in the normal subjects (610 ml./M.², 23 per cent of total blood volume), this difference is not statistically significant. The cardiac index is significantly higher and the mean transit time significantly shorter in the normal subjects than in the patients with mitral stenosis. The mean total blood volume is the same in both groups.

Exercise. The values for central blood volume, cardiac output, and mean transit time before and after exercise are shown in Tables II and III.

In the 8 normal subjects, in spite of significant elevations of cardiac output and decreases of mean transit time, the mean central circulating blood volume shows no change after exercise (620 ml./M.² before and 628 ml./M.² after exercise, 25 per cent of total blood volume in both instances).

Similarly, the patients with mitral stenosis were able to effect an increase in cardiac output and decrease in mean transit time after exercise, but showed a decrease in the mean value for central volume (618 ml./M.² before and 560 ml./M.² after exercise, 24 and 21 per cent of total blood volume before and after exercise, respectively). However, this decrease in central volume is not significant in the small sample tested.

Total blood volume showed a slight rise after exercise in both groups, but the increments were not significant: 69 ± 8 ml./Kg. before to 71 ± 9.9 ml./Kg. after exercise in normal subjects and 73 ± 11.4 ml./Kg. before to 75 ± 10.4 ml./Kg. after exercise in the patients with mitral stenosis.

Although in both groups the mean value for central volume showed no significant change after exercise, there were individual variations, as illustrated in Tables II and III and Fig. 4. It is noteworthy, however, that among the normal subjects and the patients with mitral stenosis the majority showed either no change or a decrease in central volume after the exercise test. In 2 normal subjects (C. E. and W. B., Table II) and one patient with mitral stenosis (H. D., Table III) the increase in calculated central volume after exercise was largely due to a relatively small decrease in mean transit time as compared to the findings in the majority of individuals studied. There were no other distinctive clinical or hemodynamic features in these 3 subjects.

All of the normal subjects and the patients with mitral stenosis showed a rise in cardiac output after exercise, together with a decrease in mean circulation time. However, the mean increment in cardiac output was significantly greater in normal subjects than in the patients with mitral stenosis.

Table I. Comparison summary of mean values for central circulating blood volume and associated parameters at rest in normal subjects and patients with mitral stenosis

	Cardiac index (*L./M.²/min.*)	*Mean transit time* (*sec.*)	*Central blood volume*		*Total blood volume* (*ml./Kg.*)
			ml./M.²	*% total blood volume*	
Normal subjects (25)	3.30	11.1	610	23	1.0
S.D.	±0.53	±2.5	±165	±5.9	±10.2
Patients with mitral stenosis (14)	2.57	15.8	678	27	72.0
S.D.	±0.58	±3.3	±190	±6.0	±9.8
t	4.05	4.98	1.14	1.95	0.30
p	<0.01	<0.01	0.2	>0.05	>0.5

Discussion

The theory and mathematical analysis of biphasic precordial dilution curves for measurement of cardiac output, mean transit time, and central circulating blood volume has been reported *in extenso* by Lammerant and by our laboratory.[11] This technique has also been recently applied clinically by Eich and by Love[12] in the determination of central volume in normal subjects and in patients with heart disease. The major advantages of the precordial method are its simplicity of application obviating both cardiac catheterization and arterial puncture and the attainment of central blood volume boundaries excluding the peripheral venous and arterial circulations. The exclusion of peripheral arterial sampling sites makes possible the study of the central blood volume after various stresses (exercise, drugs) uninfluenced by redistribution of arterial flow. The limitations of this technique for the measurement of cardiac output and circulation time as mentioned by Shipley[3] for wide angle counting have been improved upon by the use of well-collimated precordial counters and by the measurement of *mean* transit time rather than *peak to peak* times.

The failure of the present study to demonstrate a clear cut increase in central blood volume in patients with mitral stenosis over that in normal subjects parallels the experience of Lammerant[6] using the same technique and is similar to other dilution studies using peripheral sampling sites.[7] The enigma presented is that of a normal central blood volume in the face of clinical evidence of cardiomegaly and pulmonary hyperemia. One group of investigators has speculatively derived the hypothesis that in the presence of a normal central volume and an enlarged heart the pulmonary component of this volume must be less than normal in mitral stenosis.[1] On the other hand, another group has found an increase in central blood volume if this volume is related to cardiac output[13]; however, the ratio of central volume to cardiac output proposed by them appears to be a tautology and merely indicates that the mean transit time is prolonged in mitral stenosis. Rapaport suggested that the normal central volume in mitral stenosis is due to low cardiac output and presented preliminary data to show an increase in this volume when the output was increased by exercise. Similarly, Ball[1] has reported an increase in central blood volume after exercise in a group of patients with mitral stenosis. However, in both of these studies the central blood volume was calculated from dilution curves recorded at peripheral arterial sampling sites. Our study does not demonstrate that central volume is dependent on cardiac output in cases of mitral stenosis. All 8 of our patients had increases in cardiac output with either a decrease or no significant change in the calculated central volume.

We believe that the failure to find an increase in central blood volume in the face of the pulmonary congestion and cardiomegaly of mitral stenosis may represent a limitation of the Stewart-Hamilton dilution technique. Although by this method Schlant[8] has found a good correlation of the calculated central blood volume with a total central blood space measured by Cr^{51} tagged erythrocytes, these studies were made in dogs with noncongested lungs and normal sized hearts. A critical study of this type pertinent to pulmonary hyperemia and cardiomegaly has not as yet been made. Until data to the contrary are available, we would speculate that in the presence of pulmonary congestion a time-concentration dilution curve, although giving a reliable estimate of cardiac output, fails to measure a mean transit time representative of the total pulmonary blood volume because of the inability of the tracer material to penetrate into slow-moving or stagnant blood spaces during the primary circulation through the lung. To the extent that the calculated volume is accepted as a *circulating* volume,[7] it is appropriately and usefully studied. However, the measurement of *total* central blood volume and its major component of interest, the lung, is probably not amenable to the application of the Stewart-Hamilton method in situations of pulmonary congestion.[1] An equilibration method of estimation of pulmonary blood volume seems more appropriate. Such a technique has been used[7] but objections relative to its application in the high flow, low volume space of the lung have been raised.[1]

Like Lammerant[4] we found that the majority of the normal subjects had elevation of cardiac output after exercise without an increase in central blood volume. Lammerant in fact demonstrated a significant lowering of central volume after exercise with this technique. These demonstrations of increased cardiac output without an increase in calculated central volume are discordant with exercise studies in which

Table II Values for central circulating blood volume and associated parameters before and after exercise in normal subjects

Patient	Cardiac index (L/M²/min)			Mean transit time (sec)			Central blood volume: ml/M²			Central blood volume: % total blood volume		
	Rest	Exercise	Change	Rest	Exercise	Change	Rest	Exercise	Change	Rest	Exercise	Change
J R	2.90	5.80	+2.90	15.7	5.8	−9.9	745	560	−185	31.0	23.0	−8.0
H P	3.16	3.98	+0.82	13.8	8.8	−5.0	725	582	−143	27.0	21.0	−6.0
C E	3.25	5.58	+2.33	10.1	8.5	−1.6	543	790	+247	23.0	37.0	+14.0
A Z	3.73	4.20	+0.47	8.5	6.3	−2.2	528	437	−91	18.0	14.0	−4.0
J W	3.42	6.40	+3.00	11.6	6.1	−5.5	664	650	−14	26.0	24.0	−2.0
J F	3.14	4.45	+1.31	15.8	10.3	−5.5	870	765	−55	36.0	32.0	−4.0
W B	2.10	4.05	+1.95	10.3	10.0	−0.3	362	675	+313	16.0	27.0	+11.0
A Y	3.80	5.50	+1.70	9.1	6.2	−2.9	576	568	−8	2.0	21.0	−1.0
Mean	3.18	5.00	+1.82	11.8	7.7	−4.1	670	678	+8	25.0	25.0	0.0
S D	±0.58	±0.93		±2.9	±1.9		±145	±116		±6.6	±7.2	
% Change			+57			−35			+1			0.0
t			4 6			3.36			1.18			0.916
p			<0.01			<0.01			>0.2			>0.2

Table III Values for central circulating blood volume and associated parameters before and after exercise in patients with mitral stenosis

Patient	Cardiac index (L/M²/min)			Mean transit time (sec)			Central blood volume: ml/M²			Central blood volume: % total blood volume		
	Rest	Exercise	Change	Rest	Exercise	Change	Rest	Exercise	Change	Rest	Exercise	Change
R D	1.70	2.22	+0.52	13.2	9.4	−3.8	380	344	−36	17.0	16.0	−1.0
L T	2.12	3.40	+1.28	14.4	9.0	−5.4	512	510	−2	23.0	21.0	−2.0
M B	2.00	2.15	+0.15	15.4	11.2	−4.2	517	406	−111	22.0	15.0	−7.0
J E	2.80	4.60	+1.80	11.5	7.1	−4.4	546	545	−1	21.0	20.0	−1.0
M G	3.10	4.60	+1.50	12.4	5.7	−6.7	640	407	−233	29.0	18.0	−11.0
P W	3.70	5.00	+1.30	15.7	10.4	−5.3	978	8 0	−108	28.0	26.0	−2.0
H D	3.20	3.90	+0.70	17.7	14.8	−2.9	955	975	+20	33.0	34.0	+1.0
L M	2.20	3.10	+0.90	12.0	7.7	−4.3	428	405	−23	18.0	18.0	0.0
Mean	2.60	3.62	+1.02	14.0	9.4	−4.6	618	560	−58	24.0	21.0	−3.0
S D	±0.70	±1.09		±2.1	± 8		±226	±234		±5.6	±6.2	
% Change			+38			−34			−10			−13
t			2.23			3.68			0.52			0.98
p			<0.05			<0.01			>0.5			>0.5

Discussion

The theory and mathematical analysis of the precordial dilution curves for measurement of cardiac output, mean transit time and central circulating blood volume has been reported *in extenso* by Lammerant and by our laboratory. The technique has also been recently applied clinically by Lich[9] and by Love in the determination of central volume in normal subjects and in patients with heart disease. The major advantages of the precordial method are its simplicity of application, obviating both cardiac catheterization and arterial puncture, and the attainment of central blood volume boundaries excluding the peripheral venous and arterial circulation. The exclusion of peripheral arterial sampling sites makes possible the study of the central blood volume after various stresses (exercise, drugs) uninfluenced by redistribution of arterial flow. The limitations of this technique for the measurement of cardiac output and circulation time as mentioned by Shipley for wide angle counting have been improved upon by the use of well-collimated precordial counters and by the measurement of *mean* transit time rather than *peak to peak* times.

The failure of the present study to demonstrate a clear-cut increase in central blood volume in patients with mitral stenosis over that in normal subjects parallels the experience of Lammerant using the same technique and is similar to other dilution studies using peripheral sampling sites.[3,7] The enigma presented is that of a normal central blood volume in the face of clinical evidence of cardiomegaly and pulmonary hyperemia. One group of investigators has speculatively derived the hypothesis that in the presence of a normal central volume and an enlarged heart the pulmonary component of this volume must be less than normal in mitral stenosis.[4] On the other hand another group has found an increase in central blood volume if this volume is related to cardiac output[8]; however, the ratio of central volume to cardiac output proposed by them appears to be a tautology and merely indicates that the mean transit time is prolonged in mitral stenosis. Rapaport suggested that the normal central volume in mitral stenosis is due to low cardiac output and presented preliminary data to show an increase in this volume when the output was increased by exercise. Similarly, Ball[1] has reported an increase in central blood volume after exercise in a group of patients with mitral stenosis. However, in both of these studies the central blood volume was calculated from dilution curves recorded at peripheral arterial sampling sites. Our study does not demonstrate that central volume is dependent on cardiac output in cases of mitral stenosis. All 8 of our patients had increases in cardiac output with either a decrease or no significant change in the calculated central volume.

We believe that the failure to find an increase in central blood volume in the face of the pulmonary congestion and cardiomegaly of mitral stenosis may represent a limitation of the Stewart-Hamilton dilution technique. Although by this method Schlant has found a good correlation of the calculated central blood volume with a total central blood space measured by Cr[51]-tagged erythrocytes, these studies were made in dogs with noncongested lungs and normal sized hearts. A critical study of this type pertinent to pulmonary hyperemia and cardiomegaly has not as yet been made. Until data to the contrary are available we would speculate that in the presence of pulmonary congestion a time-concentration dilution curve, although giving a reliable estimate of cardiac output, fails to measure a mean transit time representative of the total pulmonary blood volume because of the inability of the tracer material to penetrate into slow-moving or stagnant blood spaces during the primary circulation through the lung. To the extent that the calculated volume is accepted as a *circulating* volume, it is appropriately and usefully studied. However, the measurement of *total* central blood volume and its major component of interest, the lung, is probably not amenable to the application of the Stewart-Hamilton method in situations of pulmonary congestion.[1] An equilibration method of estimation of pulmonary blood volume seems more appropriate. Such a technique has been used, but objections relative to its application in the high flow, low volume space of the lung have been raised.[1]

19 Braunwald E Fishman A P and Cournand A Estimation of volume of circulatory model by the Hamilton and the Bradley methods t arying flow olume ratios J Appl Physiol 12 445 1958
20 Mitchell J H Sproule B J and Chapman C B The physiological meaning of the maximal O_2 uptake test J Clin Invest 37 538 1958
21 Braunwald E and Kelly E R The effects of exercise on central blood olume in man J Clin Invest 39 413 1960
22 Marshall R J Significance of changes in central blood volume in man during exercise Fed Proc 19 118 1960
23 Semler J Shepherd J T and Marshall R J Pressure flow volume relationships in the pulmonary circulation of the exercising dog Fed Proc 18 141 1959

The use of intracardiac carbon dioxide in the diagnosis of pericardial disease

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This preliminary report offers confirmation of and support for the work of previous investigators demonstrating the safety and diagnostic value of intracardiac carbon dioxide in negative-contrast roentgenography. Durant, Oppenheimer, Stauffer and colleagues developed the method and demonstrated its diagnostic value. Scatliff, Kummer and Janzen recently reported on the application of the method in a series of 22 patients. The greatest value of the procedure thus far has been its use in the differentiation of the large heart of myocardial dilatation from that of pericardial disease and effusion.

With a patient in the left lateral decubitus position, carbon dioxide once in the right atrium will rise and outline the right lateral limits of this cardiac cavity while forming a gas-blood interface below. These events are demonstrated by roentgenography. One observes from the patient's right to left the aerated lung, the opaque right atrial wall or band, the bubble of carbon dioxide, and the blood level. The right atrial wall or band is composed of visceral and parietal pleura, parietal and visceral pericardium, and right atrial myocardium and endocardium. In myocardial dilatation the right atrial band shows little if any change in width. Because of the relationships of specific gravity in free pericardial effusion, the heart assumes a dependent position and the right atrial band is widened by the pericardial fluid. Some widening of this area may be seen in acute or chronic pericarditis with[out] effusion, but here the widening is frequently not so great and in addition other clues help to distinguish this from [illegible] pericardial effusion.

Materials and methods

The materials necessary for this procedure are demonstrated in Fig. 1. They consist of (1) sterile 18-gauge needle, (2) sterile plastic extension tube (a P 10 Stern[illegible] expendable plastic tube was used), (3) sterile three-way stopcock, (4) sterile 50-c.c. or 100-c.c. syringe, (5) sterile 20-c.c. syringe with normal saline, (6) suitable tubing for connection between the stopcock and the tank of carbon dioxide (the rubber tubing and glass adaptor from a routine hospital intravenous fluid set has been found to be perfectly acceptable), (7) tank

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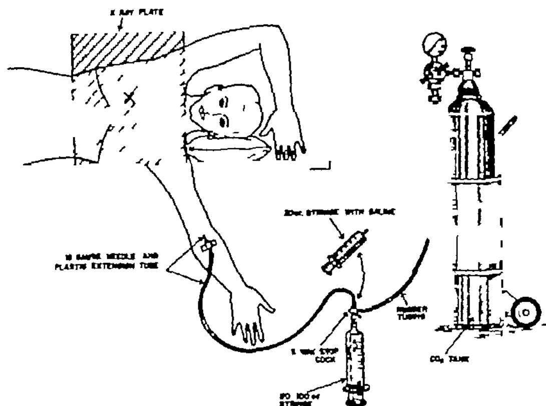


Fig. 1. Demonstration of the position of the patient and the materials necessary for intracardiac carbon-dioxide procedure.

of carbon dioxide, pure medical carbon dioxide U.S.P.* was used, and (8) ordinary roentgenographic facilities.

It is obvious that only a small amount of equipment is necessary and that storage is no problem. The smaller materials may be put up in a special tray for immediate use. The tank of carbon dioxide may be conveniently placed in an out-of-the-way corner of the x-ray room.

For purposes of simplicity the procedure recommended by others was modified. The procedure is as follows: (1) As shown in Fig. 1, the patient is placed in the left lateral decubitus position (right side up) on a suitable table in front of the 14 by 16 roentgenographic film. A vein in the antecubital region of the left arm is entered with the 18 gauge needle which is attached to the plastic extension tube and the 20 c.c. syringe filled with 0.85 per cent NaCl. The needle is kept open by periodic injections of the saline. (2) For later comparison a 6 foot roentgenogram may then be obtained before injection of carbon dioxide, but this is not absolutely necessary. Films are obtained in the anterior-posterior projection during a moderately deep, briefly held inspiration. (3) The 50 c.c. or 100-c.c. syringe and attached three-way stopcock are then quickly tested for air tightness by attempting to move the syringe plunger while the sterile gloved finger blocks the openings of the stopcock. Connection is then made to the tank of carbon dioxide and the entire apparatus is washed several times with the carbon dioxide gas by repeatedly filling and emptying the syringe. (4) The empty 50 c.c. or 100-c.c. gas syringe and the attachments that have been washed with the carbon dioxide are then connected by the stopcock to the plastic extension tube after removal of the 20 c.c. syringe. (5) The x-ray technician is then alerted, the syringe filled with the desired amount of carbon dioxide, the stopcock turned, and the gas injected intravenously as rapidly as possible. We have

*Supplied by the National Gas Company, Medical Gas Division, Chicago, Ill. (tank type G contents 3,200 gallons).



Fig 2 I tent N 1 *Left* Teleroentgenogram bowing markedly enlarged cardiac shadow nd bilateral pical pulmonary infiltrates *Upper right* I reinjection film *Lower right* I ostinjection film sh wing bubble of carl dox le deep in the cardiac h low (rrows) The ri ht tri l band me ures 41 mm in width



Fig 3 Patient No 1 *Left* Lateral decubitus show ng air i pericardial sac The thickened pericardium mea ures 17 mm in width *Right upper and lower* After jection of carbon dioxide t 4 and 8 seconds respect ely show ng air in pericardial sac *above* and carbon dioxide in right trium and ca ae *below*

used 50 to 100 c c of gas (approximately 1 c c per kilogram) but have found that 50 c c is usually suitable (6) The postinjection roentgenogram is then made We obtained films immediately 4 seconds 8 seconds and 15 seconds after the completion of the injection but a single film at 4 seconds has proved satisfactory (7) The patient is then maintained in the left lateral decubitus position for at least 10 minutes after the injection of the carbon dioxide in order to insure complete absorption of the gas from the right atrium

The entire operation requires only a few minutes The procedure is useful safe simple and causes no distress to the patient The noise of the gas entering the vein is clearly audible and with the stethoscope one may easily detect gurgling sounds due to the gas in the heart

To date the procedure has been employed 36 times in 25 patients in this laboratory

Case reports

Patient No 1 S R 49 year-old Negro man as admitted to Charity Hospital with history of several months of low grade fever malaise and loss of weight. For 4 to 5 days prior to admission there had been light dyspnea and moderate pain in the lower substernal region of the chest A teleroentgenogram revealed a markedly enlarged heart shadow and bilateral apical pulmonary infiltration more prominent on the right (Fig 2) Shortly after admission a carbon-dioxide study showed a flattened gas bubble deep in the heart shadow (Fig 2) Three days later diagnostic pericardial paracentesis was done and 200 to 300 c of cloudy yellow fluid was removed followed by instillation of 30 c.c of air in the pericardial sac A roentgenogram then revealed an air fluid level below thickened shaggy pericardium (Fig 3) A repeat carbon-dioxide study was done and again showed the bubble of carbon dioxide deep in the heart shadow in the right atrium and ... plus the air bubble in the pericardial sac (Fig 3) Subsequent cultures of the pericardial fluid were positive for tuberculosis

Patient No 2 J T 47 year-old Negro man was admitted to Charity Hospital because of findings suggestive of right and left ventricular congestive failure and definitely enlarging cardiac shadow on repeated outpatient chest ray films during the preceding year He was chronic alcoholic who gave ... very unreliable history There were record of several previous admissions for knife wound of the chest on one occasion 2 years previously this was associated with hemopericardium The possibility of chronic pericarditis was raised but subsequent carbon-dioxide study revealed thin right atrial band with rounded unflattened contour (Fig 4)

Patient No 3 E C 43 year-old Negro woman with clinical diagnosis of postpartal myocarditis had been followed up for the preceding 2 years There had been repeated episodes with findings of



Fig 4 Patient No 2 *Left* Teleroentgenogram showing mild to moderate cardiomegaly *Upper right* Preinjection film *Lower right* Postinjection film showing thin right atrial band (2 3 mm) with rounded unflattened contour



Fig 5 Patient No 3 Upper Preinject on film Lower Postinjection film showing gas in right atrium cavae and right atrial appendage (arrow) The right atrial band at the inferior arc measured 4 mm

left but especially right ventricular failure Because of globular heart shadow on x-ray examination the possibility of pericardial effusion was raised Carbon-dioxide study however revealed normal right atrial band compatible with myocardial dilatation rather than effusion (Fig 5) The films were interesting in that gas trapped in the right atrial appendage could be identified

Patient No 4 L W 33 year-old Negro woman was admitted to Charity Hospital with 5-day history of fever severe anterior chest pain and dry hacking cough The electrocardiogram was typical of acute pericarditis and teleroentgenogram on admission revealed moderately large heart shadow and bilateral light pleural effusions (Fig 6) A few days later after 3 thoracenteses little if any pleural fluids could be demonstrated roentgenographically Injection of carbon dioxide revealed a uniform widening of the right atrial band (Fig 6) suggestive of acute pericardial thickening with little or no pericardial fluid Nevertheless since the etiological diagnosis was doubtful several pericardiocenteses were attempted on two different occasions No pericardial fluid was obtained even though the needle touched the left ventricular wall several times. The subsequent clinical course of the patient was compatible with that of acute pericarditis

Patient No 5 C L 15 year-old white girl was admitted to Charity Hospital in a terminal state with long standing uremia from chronic glomerulonephritis A teleroentgenogram revealed moderately enlarged heart (Fig 7) Injection of carbon dioxide showed a somewhat flattened gas bubble deep in the cardiac shadow (Fig 7) In addition a regurgitation of the gas into the hepatic veins was demonstrated Subsequent autopsy 2 weeks later revealed slight to moderate thickening of the pericardium and a few hundred cubic centimeters of pericardial fluid

Patient No 6 W R 54 year-old Negro man is included in this series because of special interest only He had a classic clinical picture of obstruction of the superior vena cava due to mediastinal malignancy Injection of carbon dioxide outlined the dilated superior vena cava and located the site of obstruction by the tumor mass (Fig 8)

Discussion

The carbon-dioxide procedure is simple quickly performed and useful diagnostically The procedure is safe and free from gas embolism because carbon dioxide is 20 times more soluble in blood than either oxygen or air Even large doses of the gas (5 c c per kilogram) alter the carbon dioxide content of blood by only 5 to 10 volumes per cent and this is quite transient (1 to 2 minutes)[8] Change in blood pH is negligible[8,9]

The carbon-dioxide cardiography provides essentially the same information as angiocardiography with radiopaque medium and there are no allergic reactions from the former Cardiac catheterization has been advocated to substantiate suspected cases of pericardial effusion but this procedure is much less practical and far more complicated and expensive Injections of carbon dioxide may be employed safely and usefully in any institution with facilities for routine roentgenography To date no adverse reactions to this procedure have been noted in this laboratory

At present the prime indication for this procedure appears to be in patients with suspected pericardial effusion especially in those in whom differentiation from myocardial dilatation is in doubt The procedure also appears to be of value in both acute and chronic pericarditis with

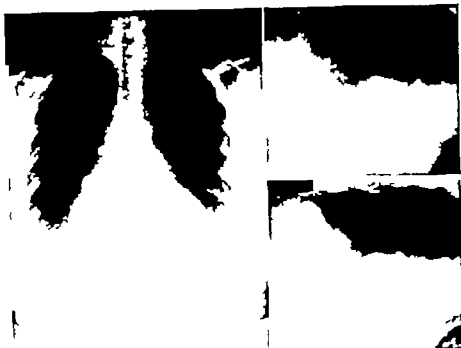


Fig 6 Patient No. 4 *Left* Teleoroentgenogram on admission showing enlarged cardiac shadow and bilateral small pleural effusion *Upper right* Preinjection film taken several days later *Lower right* Postinjection film showing carbon dioxide in right atrium and uniform thickening of right atrial band measuring 11 mm in width

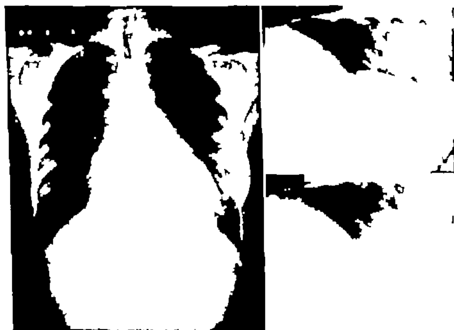


Fig 7 Patient No 5 *Left* Teleoroentgenogram showing enlarged cardiac shadow and calcified right paratracheal node *Upper right* Preinjection film *Lower right* Post injection film showing carbon dioxide deep in the cardiac shadow Gas is noted to be regurgitating into hepatic veins



Fig 8 I tie t N 6 *Upper* I rei jection film *Lower* I ostinjection film showing carbon dioxide filled superior ena ca (rrw) ending bruptly t medi stinal ma

or without effusion It c in assist in the study of some vascul ir disturb inces such as obstruction to l irge veins e g the superior ven c iv i It possibly could assist with the detection of tumors of the right atrium With larger doses of c irbon dioxide it m iy help delineate disturbances in the right ventricular outflow tract Its v lue in man with intracard ic shunts and its value in the diagnosis of peripheral v ascul ir lesions has yet to be demonstrated

There are few contraindications There is a possible contraindication in p itients with intracardiac shunts because of the danger of gas embolization to the brain or coronary arteries should the gas reach the left side of the circulation It has been demonstrated however that quite large amounts of carbon dioxide may be injected into the left ventricle of dogs with no adverse effects [3] This danger is extremely unlikely in man lying on his left side Appropriate caution is advised in patients with impaired mech ini ms for carbon dioxide excretion such as in patients with far adv inced pulmonary emphysema be c ruse of the d inger of provoking severe carbon-dioxide n ircosis [3]

One obvious contraindic ition exists in severely ill patient such as patients with marked orthopne i who might be unable to maint un the left l iteral decubitus position for the required length of time

A few prec iutions are necessary in addition to those mentioned above Of foremost import ince is th it *pure* c irbon dioxide only be employed for injection Some tanks of so c illed hospit il c irbon dioxide cont un significant amounts of oxygen Purity of the g is should be thoroughly checked with the m inuf icturer or other responsible au thorities In one inst ince g is supplied to this laboratory as pure carbon dioxide actu illy cont uned 4 per cent oxygen As an extra precaution we h ive analyzed the ga from the tank ourselves before use

From observ itions in thi laboratory and from those of others several patterns m y be recognized roentgenographically

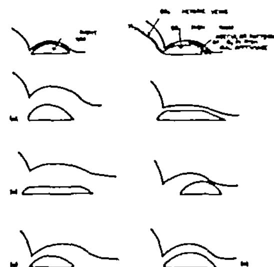


Fig 9 a The normal right trial band a noted in I tients Nos 2 and 3 *b* The normal right atrial band plus carbon dioxide in ri ht trial ppendage and in hepatic eins a noted in Patient Nos 3 and 5 re pectively The ery thick right trial band with upper convexity of gas bubble *d* Moderate to marked flattening of right atrial band The ery thick right trial band lso showing moderat to marked flattening as noted in Patient N 1 *f* and *g* Asymmetrical widening of the right trial band *h* U iform thickening of the right trial band w th upper convexity of the gas bubble noted in I tient No 4

after intravenous injection of carbon dioxide. It should be stressed, however, that our observations on patients with the diagnoses proved absolutely by operation or autopsy have been limited and the initial impressions may have to be modified in the future. Fig. 9 demonstrates several of these patterns.

The normal right atrial band. This band measures 5 mm. or less in width and is illustrated in Fig. 9 a. Patients Nos. 2 and 3 in our series are examples of the normal. At times gas may be seen in the right atrial appendage or in the hepatic veins (Fig. 9 b) as noted in Patient No. 3 and No. 5, respectively. As seen in other illustrations, gas may be also detected in the inferior and superior venae cavae.

The very thick right atrial band measuring greater than 20 mm. in width with a rounded inferior border of the atrial band (*Fig. 9 c*). This is considered[4] to be diagnostic of at least some but usually massive pericardial effusion with little if any chronic fibrotic pericardial change.

Moderate to marked flattening or straightening of the inferior surface of the right atrial band with measurements less than 20 mm. (*Fig. 9 d*). This appears to be indicative of subacute or chronic pericardial thickening with diminished distensibility. Superimposed effusion might be present.

Moderate to marked flattening or straightening of the inferior surface of the right atrial band with widening greater than 20 mm. (*Fig. 9 e*). This is suggestive of chronic pericardial thickening plus pericardial effusion. This was demonstrated in Patient No. 1. It seems unlikely that acute or chronic pericardial thickening alone would result in widening of the atrial band to over 20 mm. in the absence of effusion.[4]

Asymmetrical thickening of the right atrial band measuring 5 to 20 mm. at its widest (*Fig. 9 f and g*). This is highly suggestive of pericardial effusion with asymmetrical distribution of the fluid over the right atrium.[4]

Uniform thickening of the right atrial band measuring 5 to 20 mm. in width with a rounded superior border of the gas bubble (*Fig. 9 h*). This is suggestive of acute pericardial thickening with little superimposed effusion. This was present in Patient No. 4.

One note of caution in interpretation lies in the problem met with when a patient presents with a right pleural effusion. In such cases when the patient lies in the left lateral decubitus position, pleural fluid may gravitate down over the right cardiac border and simulate intrapericardial fluid on the carbon dioxide roentgenogram. Here one frequently must wait until the fluid disappears spontaneously or is removed after thoracentesis before proceeding with the carbon dioxide study.

Summary

The use of intracardiac carbon dioxide in negative contrast roentgenography as a diagnostic procedure in pericardial disease has been outlined. Its rationale, safety, indications, contraindications, precautions, and interpretative clues have been discussed. It is a useful, safe, simple, and rapid procedure when properly employed.

REFERENCES

1. Oppenheimer, M. J., Durant, T. M., Stauffer, H. M., Stewart, G. H., Lynch, T. R., and Barrer, F. I.: In vivo visualization of intracardiac structure with gaseous carbon dioxide: cardiovascular respiratory effects and associated changes in blood chemistry, Am. J. Physiol. 186:325, 1956.
2. Stauffer, H. M., Durant, T. M., and Oppenheimer, M. J.: Gas embolism: roentgenologic considerations including the experimental use of carbon dioxide as an intracardiac contrast material, Radiology 66:686, 1956.
3. Durant, T. M., Stauffer, H. M., Oppenheimer, M. J., and Paul, R. E.: The safety of intravascular carbon dioxide and its use for roentgenologic visualization of intracardiac structures, Ann. Int. Med. 47:191, 1957.
4. Paul, R. E., Durant, T. M., Oppenheimer, M. J., and Stauffer, H. M.: Intravenous carbon dioxide for intracardiac gas contrast in the roentgen diagnosis of pericardial effusion and thickening, Am. J. Roentgenol. 78:224, 1957.
5. Scatliff, J. H., Kummer, A. J., and Janzen, A. H.: The diagnosis of pericardial effusion with intracardiac carbon dioxide, Radiology 73:871, 1959.

The role of exercise tests in the diagnosis of coronary artery insufficiency

Pulmonary and cardiac response to a treadmill work capacity test applicable to patients convalescing from acute myocardial infarction

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This study using a treadmill walkin test was conducted to determine the per cent of recovery and hence the reproducibility of an exercise period of 10 minutes repeated after 20 minutes of rest in healthy but poorly conditioned volunteer physician subjects Because of the lack of information on cardiopulmonary parameters in the early recovery period after myocardial infarction this treadmill test was applied to a few pnt ents in an attempt to ascertain whether testing these patients is feasible The work load was kept constant by individualizing the treadmill belt speed for subjects of different wei ht The electrocardiographic response (C R leads) was continuously monitored on the oscilloscope This test was used to observe the pulmonary ventilation heart rate oxygen upt ke and the oxygen extracted from the in pired air during the exercise at a pecific work load

Potgieter[1] has summarized an earlier study of subjects undergoing a treadmill exercise test in our laboratory He reported the abnormalities of rhythm and S T seg ment displacement that were observed when the electrocardiographic response to exercise was monitored continuously on an oscilloscope during treadmill walking Since that time further studies have been made in an attempt to clarify the limitations of this type of exercise test and the significance of the associated S T segment changes These studies are a preliminary approach to a method of selecting patients who might be candidates for endarterectomy

A change in the electrocardiogram with

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exercise in patients with angina pectoris was reported in 1931 by Wood and Wolferth.[3] They raised the question whether the alterations in the electrocardiograms associated with the attacks of angina pectoris were caused by the exercise or by temporary myocardial ischemia or the changes in blood pressure and pulse rate which accompanied the attack in patients with coronary artery insufficiency. Although many studies have been made in the interim, much remains to be elucidated about the genesis of these electrocardiographic changes. Continuous monitoring of QRS-T complexes and observance of the changes from the resting observation during exercise gives no direct information on reductions either in coronary blood flow or myocardial oxygen tension or increases in cardiac oxygen metabolism.

We sought a test procedure which would allow us to make observations during a specific work load for each subject. Such a test, which if repeated either after a short rest period or on a later date, should keep the energy expenditure constant during the treadmill exercise. Having such a test procedure, it was hoped that a method of measuring coronary blood flow other than by the nitrous oxide method might be developed which could be applied to the patient during rest and repeated while the patient was in a steady state during exercise at the predetermined load. Such a method of measuring coronary blood flow during exercise which has advantages over the nitrous-oxide desaturation technique has not yet become available.[4]

The present report attempts to show the reproducibility of the test when used in 8 healthy subjects with a double exercise period of 10 minutes. Because there is a paucity of comprehensive studies of the hemodynamics after acute myocardial infarction, we also present an assessment of several cardiopulmonary parameters during exercise tests in 3 patients conducted 6 weeks to 6 months after an episode of acute myocardial infarction.

Methods

The exercise load of Dr. Bruce's treadmill test (10 per cent grade at 1.73 miles per hour for 10 minutes) was found to be tolerated by patients who were able to walk 1.5 to 2.0 miles daily in the hospital corridors, as measured by pedometers, while convalescing from the acute episode and before their discharge from the hospital.

Essentially, the technique of the test was the same as that described by Bruce.[7,8] Potgieter was able to work out a method of eliminating alternating current interference so that it was possible to obtain acceptable electrocardiographic tracings during exercise as well as a continuously depicted QRS-T complex on the Viso-Scope.* The physician responsible for the safety of the subject monitored the Viso-Scope throughout the experiment. The reports of Yu[9] and Longmire[9] indicate that this approach to evaluation of the electrocardiogram of the exercising patient was feasible in their laboratories.

The protocol of the test is shown in Fig. 1. The healthy subjects, all volunteer males between the ages of 33 and 60 years, were tested at a work load of 370 kilogram-meters per minute for 10 minutes. After a 20 minute rest period, the subjects underwent another 10 minutes of exercise at a work load of 370 kilogram-meters per minute. Individualization of the work load was made possible by using the nomogram (Fig. 2) designed by Potgieter for our treadmill† when set at a 10 degree elevation. The speed of the treadmill belt needed to give the chosen work load was selected according to the weight of the subject, and could be monitored by use of the tachometer on the treadmill. The belt speed could be adjusted over a range of 1.5 to 4.0 miles per hour.

The oxygen consumption was obtained by collecting the expired air in a Tissot spirometer and analyzing this sample for the oxygen content by the Scholander method.[11] The remainder of the parameters were recorded as reported by Bruce,[8] with electrocardiographic recording as described by Yu.[9]

Results

The data obtained in the 8 subjects are shown in Fig. 3. These observations indicate that recovery to pre-exercise values in this group of 8 healthy male subjects tended to

*Model No. 169 made by Sanborn Company, Waltham, Mass.
†Manufactured by W. E. Q. [illegible] Instrument Co., Seattle, Wash., and designated Model No. 18-49.

(70 or 550 Kg. me. m/min)

Fig. 1 Abbreviation on the left hand side of the figure: V.I. pulmonary ventilation liters per square meter per minute; H.R. heart rate; R.E. respiratory efficiency (oxygen extracted from inspired air) volume per cent; O.T. gross oxygen consumption liters per minute; ECG electrocardiogram; BP blood pressure millimeters of mercury; C.O. calculated cardiac output utilizing pulse pressure and heart rate liters per minute; A-V systemic arteriovenous oxygen difference based on Fick equation, cubic centimeters per 100 cubic centimeters. The electrocardiogram was monitored throughout the exercise period. The other parameters were measured during the fifth and the sixth minutes of exercise.

be completed within 15 to 20 minutes, two tests having been made on the same occasion. The work load was kept at 370 Kg.M. by use of the nomogram mentioned above when exercise work was performed by these subjects. Tests done on two different occasions on the same individual at the same work load showed acceptable reproducibility.

The healthy resting male was found while standing alert to utilize 4.0 ml. of oxygen per kilogram of body weight per minute. Net mechanical efficiency was about 16 per cent as had been reported by Dill and co-workers.[12] At this level of efficiency the energy expenditure approximates 100 kilogram-meters per minute. This represents the individual's "ready for action" energy expenditure level. The work load used increased the total oxygen consumption 3 to 7 times above that of the "ready for action" level.

Fig. 4 compares the average responses for 24 tests on 7 normal subjects with the average responses of 6 tests made on 3 postmyocardial patients and with 6 tests on 3 patients with primary hypertension taking depressor drugs. These tests were carried on at varying work loads. The subjects with primary hypertension being healthy were better able to exercise for 10 minutes at a higher work level approximating that of the normal subjects than were the postmyocardial infarction patients.

The resting parameters are at about the same level except for (1) narrowed pulse pressure of the postmyocardial infarction group and (2) the higher but essentially top normal systolic and diastolic pressure level of the hypertensive subjects before exercise. In the small series studied the outstanding changes are the increase in pulse pressure as well as heart rate at the higher work load in the hypertensive subjects. The postinfarction patients' average increase in heart rate is greater than that of the normal subjects but less than that of the hypertensive patient.

Comments

These observations confirm the reports of Bruce, Welch and co-workers[4,5] that the treadmill test is a stress that even postmyocardial infarction patients can tolerate without too much difficulty. With the increased work load used in these exercise tests the postinfarction patients showed an

Individualization of exercise work Kilogram Meter/Min

Fig. 2 Individualization of exercise work in kilogram meters per minute. This nomogram can be utilized to obtain the belt speed for the treadmill by relating the individual weight and work load. For a 70 kilogram man to work at 550 Kg.M./min. would require a belt speed setting of 2.9 miles per hour.

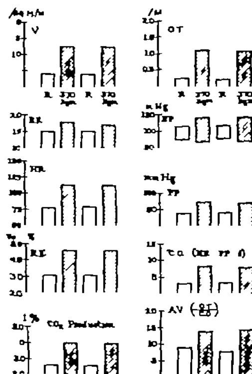


Fig 3 Average responses of 8 normal subjects tested during 2 periods of treadmill exercise at 370 kg M work loads with rest period between. Ventilation (V) liters per square meter per minute ($L/Sq\ M/min$) respiration rate (RR) heart rate (HR) respiratory efficiency (RE) carbon dioxide (CO_2) production gross oxygen consumption ($O\ T$) liters per minute (L/min) blood pressure (BP) with top of bar representing systolic pressure and bottom of bar diastolic pressure pulse pressure (PP) millimeters of mercury cardiac output (CO) as the product of heart rate pulse pressure and factor (f) liters per minute arteriovenous systemic oxygen difference (AV) as the quotient of total oxygen and cardiac output $\left(\frac{O\ T}{CO}\right)$ cubic centimeters per 100 cubic centimeters

augmentation of heart rate Turell and Hellerstein suggested that if the pulse rate during effort exceeds 135 140 beats per minute during a double two-step test of a postinfarction patient an abnormal response is indicated All of our post infarction patients tested at a work load over 200 kg M/min usually between 370 and 450 kg M min showed a heart rate during exercise of 136 or more beats per minute

Ford and Hellerstein[14] noted that in patients with arteriosclerotic heart di the amount of oxygen extracted from inspired air (R E) is reduced We also observed that on the average less oxygen was extracted from the inspired air in the postmyocardial infarction patients than in the other two groups tested

If an estimate of or a first approximation to cardiac output (CO) can be derived from the product of pulse pressure (P P) and heart rate (H R) the trend for this small sample of hypertensive males is to have a higher product or resultant than either the normal subject or the postinfarction patients during the treadmill walk as shown at the top of Fig 5 If the ratio of $\frac{\text{Total O}}{\text{C O}}$ (from the Fick equation for oxygen and cardiac output) represents systemic A V difference (A V) then the pre exercise level in the postinfarction

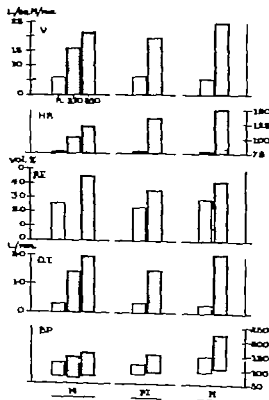


Fig 4 The effect of treadmill exercise on pulmonary ventilation (V) heart rate (HR) respiratory efficiency (RE) gross oxygen consumption ($O\ T$) and blood pressure (BP) in normal subjects (N) postmyocardial infarction (PI) and hypertensive patients (H) The unlined bars represent resting values the wide lined bars 370 kg M work load values and the narrow lined bars 550 kg M values

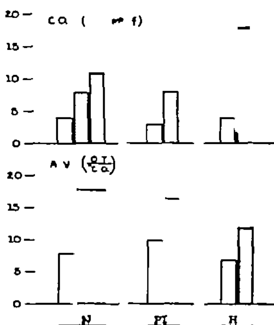


Fig. 5 The effects of treadmill exercise on derived cardiac output (*C O*) and derived systemic arteriovenous oxygen difference (A V) in postinfarction patients (*PI*) hypertensive patients (*H*) and normal subjects (*N*) The unlined bars represent resting values the wide lined bars 3 0-kg M work load values and the narrow lined bars 550 kg M work load values

patients as shown in the lower part of Fig 5 suggests that this resting A V difference is essentially the same as that in the normal group and increases with exercise about as much as that in the normal group tested

Between 300 and 600 kilogram meters all subjects on retesting showed a linear response of pulmonary ventilation total oxygen consumption and heart rate When the work performed by the three groups of subjects is considered at a gross oxygen consumption of 1 5 liters the results in Fig 6 suggest (a) postinfarction patients had a faster heart rate and performed less work (b) the amount of oxygen which they extracted (R E) from the expired air was less (c) they were unable to increase pulse pressure and (d) despite their increased heart rate their derived cardiac output C O increased about twofold as in normal subjects The effect of the increased work load (at the same total gross oxygen uptake) in the postinfarction patients was to increase the systemic A V oxygen difference A V This is to be expected since other studies have shown that certain organs extract more oxygen in order to meet the oxygen demands of the more active tissues such as the heart and skeletal muscles by encroaching upon the systemic venous oxygen reserve[6, 11, 16]

From these experimental data the only approach is an indirect one as to what might be happening with regard to the extraction of oxygen in the heart muscle[8, 16] Severe changes in mean cardiac oxygen tension affect the myocardial electrical activity[17] and one would expect this to be reflected eventually in the contraction-to-contraction depiction of the QRS-T complex on the Vaso Scope

Potgieter observed that the S-T segment changes do become apparent even at low

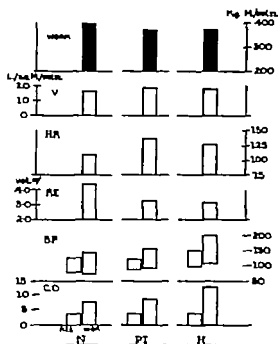


Fig 6 Bar graph indicating at the top the work load in kilogram meters per minute at a total oxygen consumption of 1 5 liters per minute for each of the three groups tested N normal subjects *PI* postmyocardial infarction patient and *H* hypertensive patients Below the work loads are V pulmonary ventilation in liters per square meter per minute *HR* heart rate beats per minute *RE* respiratory efficiency (oxygen extracted from inspired air) volume per cent *BP* blood pressure millimeters of mercury with *S* as the systolic reading and *D* the diastolic value with the unlined bars for the values at rest and the stippled bars for the readings observed at work *C O* is the derived cardiac output in liters per minute obtained from the product of pulse pressure heart rate and a factor (See text)

work loads (200 Kg M /min) before the postinfarction patients complain of substernal distress or bothersome breathing effort Because this QRS T change is considered to be an unfavorable symbol of coronary blood flow inadequacy during exercise tests on such patients were immediately terminated

In one of the postinfarction patients after about 5 minutes of exercise at a lower work level (175 200 Kg M /min) and at a time when he had no substernal distress a negative displacement of about 0 5 millivolts was recorded and the test was immediately terminated No untoward reaction ensued We have observed difficulties from day to day both in eliminating the alternating current interference and in minimizing the artefacts of muscle tremor and expansion of the chest cage during exercise This makes careful monitoring difficult These difficulties make us wary of the use of this type of exercise test response in the selection of patients for endarterectomy as has been described by Kattus and associates [9]

From these preliminary observations we believe that further studies are indicated as follows

A Clinical investigation should assess the validity of recommendations for activity of postmyocardial infarction patients by controlled treadmill work level tests These tests might produce more rational advice as to the role of walking exercise in recovery from an acute myocardial infarction

1 Patients recovering from acute myocardial infarction and with resting electrocardiograms back to normal 6 weeks to 6 months after the episode might be assessed at work loads approaching 370 Kg M /min if they can be taught to accustom themselves to lesser treadmill work

2 Using the double work period exercise test described originally by Foltz and co workers [6] and applied here to the healthy subjects might have advantages in testing the cardiopulmonary reserve and recuperative potential of the postmyocardial infarction patient 6 months or more after the acute episode

B Patients with abnormal electrocardiograms persisting 6 weeks to 6 months after myocardial infarction must be even more cautiously studied in order to determine what is the most rational prescription of walking activity

C The possible use of cinefluorography with such work tests (in an attempt to correlate any changes during the treadmill exercise in frontal surface area which was *found to be normal at rest*) might assist in the attempt to predict which convalescing infarction patients with persisting abnormal electrocardiograms are most likely to go into the postinfarction congestive heart failure syndrome if ambulated too vigorously

Summary and conclusions

1 Preliminary studies on 8 healthy male subjects show that the response of ventilation oxygen uptake and heart rate to treadmill exercise varying between 300 and 600 kilogram meters per minute is linear and reproducible

2 Patients recovering from an acute myocardial infarction if able to be ambulatory in the period 6 weeks to 6 months after the episode have been observed to be able to tolerate an exercise work load of 370 Kg M /min up to 10 minutes Our studies of testing at these work levels in selected patients show that the treadmill walk can be performed without undue apprehension excessive increases in heart rate or marked S T segment displacement in the period 6 weeks to 6 months after myocardial infarction

3 Although the beat to beat recording of the electrocardiogram is not completely satisfactory during exercise *this seems to* be as good an approximation to a measurement of coronary blood flow under these conditions as is presently available The alternative is the use of the more cumbersome nitrous oxide method as described initially by Bing Kety Eckenhoff and Goodale

REFERENCES

1 Potgieter L Schmittbenner J E Daugherty E A and Hafkenschiel J H Preliminary report on the work capacity of patients with hypertension and after myocardial infarction T & Stud Coll Physicians Philadelphia 27 88 1959

2 Wood F C and Wolferth C C Angina pectoris the clinical and electrocardiographic phenomena of the attack and their ...

the ffect of experime tal temporary coron ry oc lu ion A M A Arch I t Med 1 a339 1931
3 Fort I I Schmi tthenner J I nd Neal H C ronary blo l flow u ng radioactive idine mpared w th trou ck Circ l tion Res 9 May June 1961
4 Bing I J H lkms H K nd Regan I J M ureme t f ron ry l lood flow ua m Circul tion 22 1 1960
5 I rnlurdo I A I ose I Tresehk M I hi S nd Bing R J The ffect of xercise on n ry bl od flow my urdi l oxyg con sumption nd rdi fficienc u m C rcu l tion 71 1953
6 Turell D J I Hellc tein H K I lua t of ard function el t t perib ph I activ ties f llow ng recov ry from ac t myocardial infar t on I rog Car lio us Dis 1a237 1958
7 Bru R A Lov jov F W Yu P N C and M Dowell M E Observ tions of ardiorespir tory perform nce in norm l subject under unu ual stress during exercise A M A Arch Ind t Hyg 6 105 1952
8 Bruc R A I lu tion of f nctional capac t nd exercise toler ne of rdiac patient Mod Concept Cardiovas Dis 2 321 1956
9 Y I N C Bruce P A Lov joy F W nd M Dowell M E Variations in lectrocardio graphic re ponses during exercise Circul tion 3 368 1951
10 Longmire J I J C nnon J A nd K tt A A The surgical treatment of ngina pec toris A M A Arch Int Med 104:886 1959
11 Scholander I F A lyzer for accurate esti mation of respiratory gases n one h lf cubic cent meter samples J Biol Chem 167:235 1947
12 Knehr C A Dill D B and Neufeld W Tr ining nd t ffect on men t rest nd at work Am J I hysiol 136 148 1942
13 Wel h G F Bruce R A Bridges W C J hnson A D Lehmann J H nd Nielsen M Comparison of a new tep test with a tread mill test for the evaluation of cardiorespiratory orking capacity Am J M Sc 223:607 1952
14 Ford A B nd H llerstein H K Energy cost of the Ma ter two-step test J A M A 164 1868 1957
15 Denall I K W Exercise tudies heart dis se Mod Concepts Cardiova Dis 28:529 1959
16 Corlin R Messer J A Levine H J Neill W A and Wagman R J Coronary circula tion in health nd disease Med Cl North America 44 1181 1960
17 Say J J Kat ber A H Sheldon W F nd Gilbert C M J The effect of levartere nol on polarographic myocardial oxygen the epicardi l electrocardiogram nd contraction in nonischemic dog hearts and experimental acute regional schemia Circulation Res 8 109 1960
18 Foltz E I y A C and Barborka C J The use of double work periods in the study of fatigue and the influence of caffeine on recovery Am J I hysiol 136 9 1942

Mitral valvotomy in children

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Mitral valvotomy is a well established and common operation It is usually performed in adults and reports of the operation in the younger age groups are scanty [1-4] This may be explained by the fact that mitral stenosis is considered to be uncommon in children and by the reluctance to operate on patients who might suffer from future attacks of rheumatic fever with possible restenosis of the mitral valve

This report deals with 13 patients who were between 9 and 16 years of age at the time of operation

Case reports

Case 1 N Y 10 year-old girl born in Jerusalem had suffered from cough and attacks of breathlessness since the age of 9 years Six weeks before hospitalization there was rapid progression of the dyspnea hemoptysis occurred and she was bed ridden There as no history of rheumatic fever On admission there was cyanosis of the lips and fingers severe dyspnea t rest and congestion of the neck eins The apex beat as palpable in the sixth intercostal pace in the anterior axillary line There was right entricular plift and at the apex diastolic thrill nd rumbling diastolic murmur ere detected The mitral first nd the pulmonic second sounds were accentuated The edge of the liver as palpable 2 cm below the costal margin The pulse rate was 100 per minute and the blood pressure as 105/75 mm Hg A chest ray film showed enlargement of the left trium the right entricle and the pulmonary arteries with congestion of the lungs The ECG howed notched and peaked P w es and right entricular strain The erythrocyte sedimentation rat was 16/44 mm

After the heart failure had been controlled with digitalis and diuretics mitral alvotomy was performed The lungs were found to be edematous and a mitral orifice of 8 mm was palpated The fibrotic commissures were split with difficulty resulting in opening of 20 mm Rheumatic activity was not detected in the biopsy of the trial ppendage The postoperati course was smooth

Fiv years after operation he is symptom free and has no restriction of her everyday activities She is not receiving drug therapy

Case 2 M M a 15 year-old boy born in Morocco arrived in Israel when he was 9 years old The following year on routine examination heart murmur was detected but no history of rheumatic fever was elicited When he was 12 years old he suffered from pain the joints and subfebrile pyrexia and had an elevated erythrocyt sedimentation rat E en after this attack he remained symptom free but at the age of 15 he was hospitalized for evaluation of the cardiac condition Examination revealed a normally developed boy with light cyanosis of the lips A right entricular uplift and presystolic pical thrill were palpated The first mitral and second pulmonic sounds were accentuated A diastolic crescendo murmur and short systolic murmur (Grade 1) were heard over the apex The pulse was 78 and regular the blood pressure was 100/70 mm Hg There were no signs of peripheral enous congestion Routine laboratory tests ga findings within normal limits Chest ray examination demonstrated enlargement of the

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All th valvot mies were performed by D M l d ky

Table I. Preoperative findings in 13 patients

Case	Sex	Age at operation (yr.)	History of rheumatic activity	Symptoms which led to operation: Palpitation and dyspnea	Hemoptysis	Grade of murmur	Degree of mitral regurgitation (grade)	X-ray findings	ECG
1	F	10	−	++	+	++++	−	LA+ RV+ LA+ pulmonary congestion	P+ RVS
	M	15	+	−	−	−	1	LA+ RV+ LA+ pulmonary congestion	P+
3	F	16	Chorea	+++	−	+++	−	LA+ RV++ LA+	P+
4	F	1	++	++	−	++++	−	LA+ LA+ LA+ LA+	P+ RVS
5	F	11	++	−	−	+++	−	LA++ pulmonary congestion	RVS
6	M	9	+	++	−	++++	1	RV+	P+ RVS
	M	15	−	−−	+++	++++	−	LA+ RV+ LA+ pulmonary congestion	P+ RVS
8	F	13	+	+++	+	++++	−	LA++ RV+ LA+	P+ RVS
9	M	15	−	+	+++	++	−	LA++ RV++ hemosiderosis	P+ RVS
10	F	10	+	+	−	+	−	LA+ LA+ LA+	RVS
11	M	14	−	−	−	−	3	LA++ LA+ RV+ LA+	LVS
1	F	14	+	+	−	++	2	LA+++ LA+ LA+ LA+	RVS
13	F	16	++	++	−	++++		LA+ RV+ LA+	P+

P+ ... had peaked and enlarged P waves in standard leads. RVS, Right ventricular strain.

left atrium, right ventricle and pulmonary arteries and congestion of the lung fields. The ECG revealed mitral P. Direct puncture of the left atrium demonstrated a mean pressure of 26 mm. Hg. At operation a mitral opening of 8 mm. was found. The cusps were fibrotic, particularly in the region of the posterior commissure. The commissures were split and 20 mm. opening was realized. Histology of the left atrial appendage showed active and healed rheumatic activity.

Five years after operation he is completely symptom free.

Case 3. R. L., a 16-year-old girl born in Jerusalem, suffered from chorea at the age of 9 years, but was asymptomatic until 3 months before hospitalization, when she began to suffer from severe dyspnea and palpitations on effort and orthopnea. Clinical examination revealed a slightly cyanotic girl. The apex beat was palpable in the fifth intercostal space and a diastolic thrill and murmur were found at the apex. The mitral first and the pulmonic second sound were accentuated. The edge of the liver was palpable 4 cm. below the costal margin. The pulse was 80 and regular; the blood pressure was 9?/60 mm. Hg. Chest x-ray examination showed enlargement of the left atrium, right ventricle and pulmonary artery. The ECG showed notched P waves.

After the patient had been treated with digitalis and antibiotics, mitral valvotomy was performed. The mitral orifice was 10 mm. in diameter with thickened leaflets and fibrotic commissures. Only the anterior commissure was split, resulting in an opening of 5 mm. without production of regurgitation. Histology of the atrial appendage showed no rheumatic activity. The postoperative course was uneventful. Her exercise tolerance has definitely improved and 4 years after operation she is working an 8-hour day as a seamstress. During the follow-up period bilateral bronchiectasis has been detected, which has necessitated continuous prophylactic antibiotic therapy.

Case 4. E. Z., a 12-year-old girl born in Morocco, had been hospitalized several times during the 5 years prior to the hospitalization now reported because of recurrent attacks of rheumatic fever. During the last year she had been unable to attend school because of palpitations and dyspnea on effort. Physical examination showed an ill-nourished, cyanosed girl, slightly dyspneic at rest. A tapping apex beat was located in the fifth intercostal space in the midclavicular line. A right ventricular uplift and an apical diastolic thrill were felt. The first mitral and the second pulmonic sound were accentuated, and a rumbling diastolic murmur was heard over the apex. The edge of the liver was palpable 2 cm. below the costal margin. The pulse was 82 and regular; the blood pressure was 90/?0 mm. Hg. Chest x-ray examination demonstrated enlargement of the left atrium, both ventricles and the pulmonary artery; the lungs were congested. The ECG showed notched and peaked P waves and right ventricular

strain. The erythrocyte sedimentation rate was 15/79. Antistreptolysin O titer was 40 units and C-reactive protein was negative.

After preparation with digitalis, diuretics, and antibiotics, mitral valvotomy was performed and a 5 mm orifice was split to 20 mm. Left atrial biopsy revealed active rheumatic myocarditis. The postoperative course was uneventful, and 4½ years after operation she is completely symptom free and leading a normal active life.

Case 5. S. E., a 13-year-old girl born in Iraq, had been hospitalized 4 times since the age of 8 years because of recurrent attacks of rheumatic fever. Since the age of 12 she had suffered from progressive shortness of breath on effort, and this, together with signs of smouldering rheumatic activity, was the reason for this fifth admission to hospital. Examination revealed a well-developed girl with venous pulsation in the neck. The apex beat was palpable 2 cm. outside the midclavicular line in the fifth intercostal space. A diastolic apical thrill was felt. Auscultation revealed accentuated first mitral and second pulmonic sounds and an apical diastolic murmur. There were no signs of peripheral venous congestion. The pulse rate was 60 per minute and the blood pressure was 90/45 mm. Hg. Routine laboratory tests gave findings within normal limits. A chest x-ray film indicated enlargement of the heart, mainly of the left atrium, and engorgement of the pulmonary vasculature. The ECG showed right ventricular strain. Catheterization of the right heart revealed markedly elevated pressures. After she had been treated with steroids, digitalis, and diuretics, mitral valvotomy w

Table II. Hemodynamic data in 7 patients preoperatively

Case number	Right atrial pressure—Mean (mm. Hg)	Right ventricular pressure (mm. Hg)			Pulmonary arterial pressure (mm. Hg)			Wedge pressure—Mean (mm. Hg)	Left atrial pressure—Mean (mm. Hg)
		Systolic	Diastolic	Mean	Systolic	Diastolic	Mean		
4	—	—	—	—	—	—	—	—	26
5	3	70	2	32	75	35	50	20	—
6	—	—	—	—	—	—	—	—	31
7	7	50	5	20	46	26	30	24	—
9	5	84	4	47	87	38	57	25	—
11	—	—	—	—	—	—	—	—	33
13	9	42	8	30	50	25	38	20	—

Table III. Operative findings and postoperative course in 13 patients

Case number	Size of opening and condition of valve	Left atrial biopsy finding of rheumatic activity	Postcommissurotomy syndrome	Duration of follow-up period (yr.)	Operative results	Remarks
1	8 mm., fibrotic	—	—	5	Very good	—
2	8 mm., fibrotic	+	—	5	Permanently symptom free	—
3	10 mm., fibrotic	—	—	4	Very good	Bronchiectasis
4	3 mm., fibrotic	+	—	4	Very good	—
5	10 mm., elastic	+	—	4	Very good	—
6	15 mm., regurgitation+	+	—	?	?	Lost to follow-up
7	5 mm., calcified	—	—	2½	Good	Fibrillating
8	3 mm., calcified	—	—	2	Good	—
9	12 mm., calcified, regurgitation+	+	—	2	Improved	Recatheterized
10	10 mm., severely deformed, fibrotic	+	—	2	Good	—
11	20 mm., regurgitation+++	+	+	2	Unchanged	—
12	15 mm., fibrotic, severely deformed, regurgitation++	—	+	1	Unimproved	Fibrillating
13	12 mm., fibrotic, regurgitation+	—	—	1	Good	—

[illegible] weeks after [illegible] she [illegible] hospitalized [illegible] of the [illegible] picture [illegible] [illegible] 6 months later [illegible] [illegible] left atrial [illegible] improved.

Case 11 [illegible] 11-year-old girl [illegible] at the age of 8 years. During her [illegible] she had [illegible] of tonsillitis [illegible] accompanied by fever. [illegible] the age of 7 years she had experienced [illegible] palpitations [illegible] effort. At the age of 11 she was hospitalized for rheumatic fever. [illegible] right heart [illegible] she suffered from intermittent [illegible] [illegible] she received [illegible] hospital for [illegible] [illegible] A presystolic thrill was palpable [illegible] the [illegible] The first [illegible] pulmonic [illegible] A presystolic [illegible] murmur [illegible] systolic murmur (Grade 2) [illegible] the [illegible] edge of the [illegible] palpable 2 [illegible] below the [illegible] margin. The [illegible] sedimentation [illegible] 36/72. [illegible] were within normal limits. The ECG [illegible] not [illegible] X-ray examination demonstrated enlargement of the left atrium, right ventricle, and pulmonary artery. After preparation with corticosteroids she was operated upon. A mitral regurgitant jet was palpated and the [illegible] mm [illegible] split to 25 mm without apparent increase of the regurgitation. [illegible] of the [illegible] period she showed no signs of [illegible] rheumatism.

One year after operation on limited activity, the condition is satisfactory [illegible] she had no rheumatic exacerbation.

Discussion

The 13 cases described in the foregoing section constitute 7.5 per cent of the mitral valvotomies performed in our service. This is an unusually high incidence. Angelino and associates, who advocate commissurotomy in children and adolescents in selected cases, report on 11 operations performed in this age group out of a total of 600 valvotomies. Glover, in a series of 1,500 cases of mitral valvular disease, found valvotomy indicated in less than a dozen instances in patients under the age of 18 years. Bailey and Bolton,[8] in a series of 1,000 commissurotomies, report on only 13 patients under the age of 20 years. They record the youngest patient operated on for rheumatic mitral stenosis as a 4½ year old girl. The prevalence of mitral stenosis in the young reported here may be explained by the high incidence of rheumatic fever in Jewish children,[7] particularly in Jerusalem. Eight of our children were either born in Jerusalem or lived there from an early age. The records of the pediatric department of this hospital show that the first attack of rheumatic fever occurred below the age of 5 years in 20 per cent of 122 patients hospitalized for this disease, contrary to the generally accepted observation that rheumatic fever is rarely seen below the age of 6 years. This very early appearance of rheumatic fever may account for the relatively early occurrence of valvular damage in our population.

The clinical picture presented by the 13 children was very similar to that seen in adults. Palpitation and difficulties in breathing were the presenting symptoms in nearly all cases. In addition, 5 patients presented with hemoptysis, which was massive in 2 cases (Cases 7 and 9). In these 2 patients the bleeding resembled the paroxysmal pulmonary hemorrhage described by Oppenheimer and Schwartz in 1933 and later called pulmonary apoplexy by Wood. A striking feature was the severe, rapidly developing incapacitation suffered by 7 of the children. Despite the absence of confirmatory laboratory tests, their rapid deterioration was suggestive of continuous rheumatic activity, but in only 3 of these patients were Aschoff bodies found in the left atrial appendage. There were 4 other patients who had positive left atrial biopsies, and in these there was neither clinical nor laboratory evidence of rheumatic activity. In 4 patients right heart catheterization was performed preoperatively and elevation of the pulmonary arterial pressure was determined. Because of suspected concomitant mitral incompetence, direct left atrial puncture was performed in 3 children and the mean atrial pressure was found to be between 26 and 33 mm. Hg. Even in the symptom-free patients, marked x-ray and electrocardiographic changes were evident. When clinical symptoms and/or hemodynamic changes of mitral stenosis are progressive, we believe that the presence of rheumatic activity does not contraindicate mitral valvotomy in selected cases, even in young children. Two patients (Cases 5 and 13) suffered recurrences of clinical rheumatic activity during a period of 5 years

despite prophylactic penicillin therapy. Both were operated on during a phase of clinically low grade activity after preparation with steroids. During a postoperative period of 4 and 1 years respectively, neither patient has had rheumatic flare up and both have been symptom free. This tends to support the opinion of Bradlow and Crawshaw that mitral stenosis in itself may be a more dangerous condition than rheumatic fever. The severe valvular deformity, fibrosis and calcification found in these children at operation suggest that the pathophysiologic changes which occur in children are in no way different from those in adults and may occur after only a few years of illness.

The patients were followed up regularly once in 6 months: a history was obtained, physical and chest x-ray examinations were performed, and an electrocardiogram was recorded. In the 12 patients whom we have been able to follow up, we have no evidence of reactivation, exacerbation, or aggravation of the rheumatic activity. All have been kept on prophylactic penicillin therapy. Two patients (Cases 11 and 12) presented the postcommissurotomy syndrome, a condition not proved to be of rheumatic origin. The incidence of this syndrome was about the same among the children as among the adults operated on in our hospital.[13] No restenosis has occurred during a follow up period of up to 5 years. The postoperative course of these children was usually smooth and there was no mortality. It was most gratifying to observe the rapid physical and mental development of most of the children after operation, particularly since some were underdeveloped preoperatively. Two patients with regular rhythm before the operation now have fibrillation, which has resisted all attempts at conversion.

Summary

Report is made of 13 children between the ages of 9 and 16 years who underwent mitral valvotomy. The clinical hemodynamic and pathologic findings were the same as those in adults. The operative results were satisfactory; 9 children showed definite clinical improvement. No rheumatic reactivation or restenosis has occurred during a follow up period of 1 to 5 years.

In our opinion, progressive mitral stenosis should be relieved surgically, whatever the age of the patient.

REFERENCES

1. Lurie, P. R., and Shumacker, H. B.: Mitral commissurotomy in childhood, Pediatrics 13:454, 1954.
2. Bradlow, B. A., and Crawshaw, G. R.: Mitral valvotomy in the younger age group, South African M. J. 29:639, 19
3. Angelino, P. F., Levi, V., Brusca, A., and Actis Dato, A.: Mitral commissurotomy in the younger age group, Am. Heart J. 51:916, 19 6.
4. Gray, I. R.: Mitral valvotomy in the young, Lancet 2:1263, 1958.
5. Glover, R. P.: Mitral surgery in young girl, Am. J. Cardiol. 4:132, 1959.
6. Bailey, C. P., and Bolton, H. E.: Criteria for and results of surgery for mitral stenosis, New York J. Med. 56:357, 1956.
   Brand-Aurban, A.: The epidemiology of rheumatic fever in Israel, Harefuah 38, 1959.
8. Ezer, A., Braun, K., Szabo, M. A., Sbor, S., and Schwartz, A.: Prevalence of rheumatic heart disease among elementary and secondary school pupils in Jerusalem, Harefuah 58:254, 1960.
9. Keith, J. D., Rowe, R. D., and Vlad, P.: Heart disease in infancy and childhood, New York, 1958, The Macmillan Co., p. 612.
10. Oppenheimer, B. S., and Schwartz, S. P.: Paroxysmal pulmonary hemorrhages syndrome in young adults with mitral stenosis, Am. Heart J. 9:14, 1933.
11. Wood, P.: Appreciation of mitral stenosis: clinical features, Brit. M. J. 1:1051, 1954.
12. Dresdale, D. T., Ripstein, C. B., Guzman, S. V., and Greene, M. A.: Postcardiotomy syndrome in patients with rheumatic heart disease, Am. J. Med. 21:57, 1956.
13. Rosenberg, S. Z., Braun, K., and Stern, S.: Postcommissurotomy syndrome, Harefuah 53:1, 195

Experimental and laboratory reports

Acute circulatory effects of arterial bleeding as determined by indicator-dilution curves in normal human subjects

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Blood volume is recognized as an important factor in cardiac regulation. In oligemic shock, cardiac output is clearly reduced. Acute expansion of plasma volume in normal human beings and in patients with mitral stenosis elevates cardiac output and stroke volume. However, previous studies of cardiac output utilizing the Fick principle and an assumed steady state have shown conflicting results after venesection in man. After removal of 420 ml. of blood, McMichael and Sharpey-Schafer[3] reported considerable reduction in cardiac output. Warren and colleagues,[4] however, failed to demonstrate significant acute changes in blood flow after depletion of blood volume by 300 to 900 ml. in 12 normal men. Cardiac output, as approximated by the ballistocardiogram, showed little variation after a phlebotomy of 500 ml., but a significant fall was noted when 1 liter of blood was removed. In the anesthetized dog, hemorrhage is accompanied by a transient fall in cardiac output and stroke volume.

The distribution of blood volume is probably of significance in the regulation of cardiac output. Sjöstrand[8] has proposed the concept of a depot in the pulmonary circulation which can be mobilized to increase stroke volume and cardiac output in response to systemic demand. The hemodynamic effects of postural changes in human beings may be explained in part by the influence of gravity on the central blood volume (CBV).

Since hemodynamic responses to depletion of blood volume in man have not been clearly established, the acute circulatory effects of arterial bleeding in normal subjects were investigated. An indicator-dilution technique was used to measure cardiac output, since this minimized the requirements for a steady state and also afforded some insight into the distribution of blood volume.

Material and methods

Nineteen male volunteers who ranged in age between 21 and 33 years served as subjects. All of them were normal by history, physical, chest x-ray, and electrocardiographic examinations. Studies were performed while the subjects were lying supine and breathing room air. No premedication was given. A No. 6 or 7 cardiac catheter was introduced into the right atrium via a right antecubital vein. A No.

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$$(1) \quad TSR\ (dynes\ sec\ cm^{-5}) = \frac{Mean\ Arterial\ Pressure\ (mm\ Hg) \times 1332 \times 60}{Cardiac\ Output\ (L/min)}$$

17T Cournand needle was placed in the left brachial artery

With a calibrated syringe 15 mg of Evans blue dye was rapidly injected into the right atrium via the catheter Samples of arterial blood were collected in 10 by 75 mm glass tubes which contained a few granules of dried heparin These tubes were placed upright in a motor-driven collecting device adjusted so that each tube sampled arterial blood for 2 seconds A sample of arterial blood was collected 10 minutes after the injection of the dye for estimation of plasma volume An electrocardiogram was recorded during each dye curve

By means of the arterial cannula 7 or 8 ml of blood per kilogram of body weight were withdrawn in about 8 minutes The blood was collected in standard vacuum donor bottles which contained 120 ml of A C D Solution B anticoagulant† A second indicator-dilution curve was obtained immediately after the arteriotomy in the manner described above The blood was replaced at the termination of the procedure

Right atrial and brachial arterial pressures were recorded immediately after each dye curve by means of Statham P23D strain-gauge transducers and a direct writing Sanborn recorder The zero reference point was taken to be 10 cm anterior to the spine Mean pressures were determined planimetrically from their phasic records

Samples of blood were centrifuged at 2 260 G for 30 minutes Optical densities of undiluted plasma in microcuvettes were read twice at 620 millimicrons in a Beckman Model DU spectrophotometer Indicator-dilution curves were constructed from the plasma concentration of Evans blue dye and plotted on semilogarithmic graph paper Cardiac output mean transit time and CBV were calculated by the Hamilton method as modified by Lilienfield and Kovach [11] The mean transit time from the right atrium to brachial artery was determined by substracting the transit time of the collecting catheter from the calculated mean transit time of the dye curve The total systemic resistance was calculated from Equation 1 (*top of page*)

Changes in the variables were statistically analyzed by the student t test [12] Correlation coefficients were obtained on all data by means of an IBM 650 digital computer

Results

The measured and calculated data obtained before and immediately after arterial bleeding of 460 to 900 ml are presented in Table I and Fig 1 correlation coefficients are shown in Tables II and III

1 Changes in volume and distribution Initially the average CBV was 1 567 ml or 26 2 per cent of the average total blood volume Immediately after bleeding there was a small but significant (p = 004) reduction in CBV to 1 455 ml Since the latter volume amounted to 27 per cent of the total blood volume there was no gross

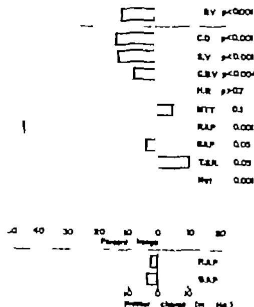


Fig 1 Changes after bleeding expressed as per cent change (above) and mm Hg (below) T B V Total blood volume C O Cardiac output S V Stroke volume C B V Central blood volume H.R Heart rate M T T Mean transit time R.A P Right atrial pressure B A P Brachial arterial pressure T S.R. Total systemic resistance Hct Hematocrit

*Warner Chilcott Laboratories.
†C ... Laboratories.

Tabl 1 Hen odvramıc data belo e and after arterıotomy

S ct (B 1 I	T al l d l me (L)	Cardıa out ıt (I mın	H t beıt m)	S ok ıe (ml)	M t ıt t ne (sec	Cer lIood ıe (I)	Art l l ıt ( )	M ın gh al ıl pre (mm Hg)	Mea l ach ıl er al p sure (mm Hg)	T al y temıc ei tı nce (dyn ı ec cm -5)
1 W A	(5 3	1	81	95	8 (	1 10	43 5	6 3	93 0	90
(1 81)	( ) 4 41	(5	4	101 2	10 3	1 1	43 5	3 3	93 0	903
S F H	(6 41	6 1	50	1 2 3	1 0	1 4	41 0	7 1	87	1 134
(2 04)	( ) 83	5)	5	109	16 5	1 (1	3 5	4	83 8	1 121
3 W C	(5 16	5 (	(	91 3	14 2	1 1	41 5	5 1	8(0	1 15
(1 84)	( ) 4 6	5 18	(1	84 9	13	1 18	44 5	1 6	85 3	1 1
4 T S	((11	9 91	5	132 1	10	1	4(0	0	9(0	5
(1 93	(5	8 9	4	1 1	10)	1 (3	41 5	1 0	6 0	6 (
5 C A	(5 81	9 1	2	127 9	11 3	1 3	49 0	1 1	(0	6(
(1 85	(6	5 80	(1	9 1	1(0	1 5	48 0	0 5	80 0	1 103
6 S T H	( ) 6 24	6 61	60	111 1	15 9	1 5	4(0	8 1	93	1 195
(2 04)	((9	6 5	57	114 1	16 8	1 83	43 5	5 7	99 4	1 214
S M	( ) 6 33	8 (	66	125	15 8	1	48 0	3 4	8(0	813
(2 12)	( ) 5 7	7 37	64	115 7	16 5	2 03	4 5	1 1	81 8	0
8 P B	( ) 4 (5	8 0	60	131	11 4	1 53	50 5	4	10(5	1 058
(1 90)	( ) 4 0	14	2	99 4	11 2	1 33	50 5	1 8	10 0	1 143
9 J C K	( ) 06	(0	6	0	13)	1 33	43 2	5 0	86 0	1 13
(1 0)	( ) 6 49	5	67	8	14 3	1 32	4 0	4 5	90 0	1 297
10 J T K	( ) 00	45	59	12(3	15 (	1 94	41 0	4 3	81 0	90
(04	( ) 6 41	6 6	51	129 8	1 8	1 9	43 5	3 5	91 4	1 105
11 F H T	(6 30	8 10	(	10 1	1 0	1 62	50 0	3 4	103 2	1 019
(2 0	(5 1	6 87	7	89 7	1	1 40	50 0	0 4	95 0	1 141

) Contr 1 A er arteriot my

alteration in the distribution of blood between the central and peripheral reservoirs

2 Changes in flow Arterial bleedin produced a significant decrease in cardiac output and stroke volume (p < 001) The changes in cardiac index were correlated with the change in stroke index (r = +0 63) but not with the heart rate which remained unchanged in most instances A significant correlation (r = +0 60) was noted between the changes in stroke volume and CBV (Fig 2) Neither the heart rate nor mean transit time changed significantly yet there was a high correlation between heart rate and mean transit time before bleeding (r = +0 87) The largest change in heart rate was in Subject 1 R who experienced transient symptoms of acute circulatory collapse characterized by bradycardia pallor hypotension and sweating 6 minutes prior to the second dye curve

3 Changes in pressure and resistance Right atrial pre ures decreased in all but one subject from an avera e of 4 3 to 2 4 mm Hg These changes were not correlated with changes in either stroke volume or cardiac output Only a mall fall of 4 mm Hg in mean brachial arterial pressure was noted The total systemic resistance increased 11 per cent (p = 03) probably due to lowered cardiac output The changes in cardiac index and systemic re istance were highly correlated (r = −0 70) (Fig 3)

Discussion

Accompanying the reduction in total blood volume by the experimental procedure of arterial bleeding was a proportionate decrease in central blood volume (CBV) and a fall in stroke volume. Since there was no compensatory increase in heart rate under these experimental conditions cardiac output showed a corresponding decrease. The changes in stroke volume were directly correlated with the changes in CBV (p < 001) (Fig 2). prior to bleeding there was a similar albeit less significant (p < 01) correlation between these parameters. These observations are in accord with those of Johnson[13] on the effects of anesthesia as well as those of Wessler and associates[14] on the cardiac response to postural changes and to antigravity suits. The inotropic effect of isoproterenol is also associated with an enhancement of CBV.[4] Thus under several experimental conditions in man the stroke output of the heart has shown a close relationship to the CBV supporting the concept of a central blood reservoir as a determinant of left ventricular diastolic filling.[9]

In the present study there was no significant correlation between the changes in cardiac output and CBV with removal of blood. Although cardiac output is utilized

Table I Hemodynamic data before and after arteriotomy—Cont'd

Subject (BSA M²)	Total blood volume (L)	Cardiac output (L/min)	Heart rate (beats/min)	Stroke volume (ml)	Mean transit time (sec)	Central blood volume (L)	Arterial hematocrit (%)	Mean right atrial pressure (mm Hg)	Mean brachial arterial pressure (mm Hg)	Total systemic resistance (dynes sec cm⁻⁵)
1 M P	( ) 4 31	7 8	67	116 5	9 8	1 28	53 5	5 2	96 4	986
(1 84)	( ) 3 71	6 83	73	94 0	9 3	1 06	49 5	0 7	89 0	1 042
13 W L	( ) [illegible] 41	7 34	[illegible]2	10[illegible] 4	10 5	1 28	43 0	3 0	84 0	916
(2 06)	( ) 4 81	6 52	80	81 8	11 8	1 28	43 0	2 0	85 0	1 043
14 E M T	( ) 5 91	9 64	71	135 8	10 3	1 65	42 0	—	95 5	93[illegible]
(2 03)	( ) 5 31	9 82	[illegible]6	129 2	9 0	1 47	41 0	—	92 6	754
15 P H	( ) 5 90	6 17	52	119 8	16 7	1 [illegible]2	44 5	4 0	92 4	1 198
(2 08)	( ) [illegible] 29	5 33	52	103 5	13 3	1 18	44 5	4 5	81 9	1 279
16 D F	( ) 9 11	9 60	76	176 3	10 0	1 60	44 5	4 0	98 8	8[illegible]3
(2 11)	( ) 8 52	7 71	80	9[illegible] 8	10 2	1 31	43 0	1 4	89 3	9[illegible]6
17 C H	( ) 6 16	10 62	8[illegible]	128 9	[illegible]8	1 38	48 0	4 7	112 8	850
(1 88)	( ) 5 53	8 73	[illegible]4	117 2	10 0	1 45	46	0 9	95 1	899
18 L P	( ) 3 [illegible] 4	8 13	[illegible]8	104 2	10 4	1 41	41 0	2 6	86 0	846
(1 98)	(a) 2 9	5 9	66	89 7	14 2	1 40	39 5	2 3	73 1	988
19 L C	( ) 6 24	[illegible]4	69	105 3	11 3	1 41	4[illegible] 5	5 7	84 0	899
(20[illegible])	( ) 5 34	5 93	72	82 4	12 8	1 [illegible]	47 5	[illegible]2	88 0	1 187
Mean	(c) 5 96	7 89	65	116 1	12 3	1 57	45 8	4 3	9[illegible] 2	954
± S D	1 70	1 38	9 0	14 2	2 7	0 26	3 3	1 7	[illegible]9	157
Mean	( ) 5 36	6 87	68	10[illegible] 1	13 0	1 46	44 9	2 4	88 5	1 053
± S D	1 70	1 24	9 1	15 2	2 7	0 76	3 2	1 6	7 6	169 5
Mean change	−0 60	−1 02	0	−14 0	+0 7	−0 11	−[illegible]	[illegible]9	−3 7	[illegible]
P	<0 001	<0 001	0 77	<0 001	0 10	0 004	[illegible]	[illegible]01	0 05	

(c) Control (a) A[illegible] [illegible]rion [illegible]my

Table II Correlation coefficients of control values

Parameter	Total blood volume index	Cardiac index	Heart rate	Stroke index	Central blood volume index	Mean transit time	Right atrial pressure	Brachial arterial pressure	Total systemic resistance
Total blood volume index		0.0	0.05	0.0	0.19	0.09	0.18	0.06	−0.09
Cardiac index			0.73	0.69	0.06	−0.7	−0.50	−0.4	−0.9
Heart rate				0.01	−0.19	−0.87	−0.31	0.23	−0.67
Stroke index					0.49	−0.2	−0.40	0.1	−0.47
Central blood volume index						0.5	−0.25	−0.13	−0.19
Mean transit time							0.1	−0.15	0.55
Right atrial pressure								0.08	0.60
Brachial arterial pressure									0.12

Coefficients greater than 0.60 underlined

Table III Correlation coefficients of change after arteriotomy*

Changes	Total blood volume index	Cardiac index	Heart rate	Stroke index	Central blood volume index	Mean transit time	Right atrial pressure	Brachial arterial pressure	Total systemic resistance
Total blood volume index		0.42	0.13	0.34	0.05	−0.28	−0.32	−0.07	−0.40
Cardiac index			−0.06	0.63	0.19	−0.63	−0.20	0.08	−0.0
Heart rate				−0.68	−0.53	−0.30	−0.02	0.26	0.18
Stroke index					0.60	−0.01	−0.18	0.03	−0.43
Central blood volume index						0.55	−0.12	0.14	−0.06
Mean transit time							0.24	0.22	0.63
Right atrial pressure								0	0.41
Brachial arterial pressure									0.63

Coefficients greater than 0.60 underlined

in the calculation of CBV the other parameter which appears in the formula (mean transit time) is an independent variable and as discussed by Rapaport and associates[15] a correlation between cardiac output and CBV is not an inherent mathematical certainty. The data reported here as well as the above mentioned studies indicate that the principal correlation is that between stroke volume and CBV rather than between cardiac output and CBV. Recent studies in patients with the chronic hypervolemia of polycythemia vera have shown excellent correlation between total volume and resting stroke volume.[1]

Another consequence of the reduced vol

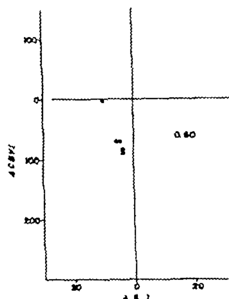


Fig 2 Relationship between the changes in stroke index and central blood volume per square meter

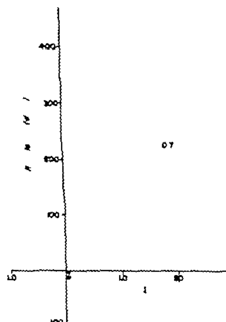


Fig 3 Relationship between the *changes* in cardiac index and systemic resistance

ume of blood was a fall in right atrial pressure This change however was not correlated with the change in blood flow or stroke volume This is in accord with the observations made by Holt[7] on anesthetized dogs in which the changes in stroke volume were correlated with the changes in left ventricular end diastolic volume but not with effective end diastolic pressure Since neither end diastolic nor effective filling pressures were measured in the subjects reported here it is beyond the scope of this paper to evaluate the significance of measurements of pressure in relation to the Frank Starling law of the heart The effect of the removal of blood on stroke volume and CBV however is in accord with this principle

The significant inverse correlation between the changes in cardiac output and systemic resistance is related to a negligible fall in blood pressure although this is interpreted as representing a compensatory mechanism to maintain systemic pressure and facilitate optimal perfusion a causal relationship cannot be established from these studies A primary role of peripheral resistance in regulating cardiac output has been advanced by Hamilton [7]

Summary

1 Arterial bleeding of 460 to 900 ml in 19 normal young male adults produced an immediate and significant reduction in cardiac output stroke volume and central blood volume (CBV) Only minor alterations were noted in heart rate or brachial arterial pressure Small elevations in mean transit time and total systemic resistance were observed

2 The central blood volume decreased in proportion to the total blood volume suggesting no significant redistribution of blood volume after arteriotomy

3 A significant correlation was observed between the changes in stroke volume and central blood volume supporting the concept of a central reservoir in maintaining stroke volume

4 The changes in systemic resistance were inversely related to changes in cardiac output

5 Although a fall in right atrial pressure occurred after arteriotomy it was not correlated with changes in cardiac output or stroke volume

REFERENCES

1 Cournand A Riley R L Bradley S F Breed F S Noble R P Lauson H D Gregersen M I and Richards D W Studies of the circulation in clinical shock Surgery 13 964 1943

2 Schnabel T G Fitzpatrick H Thomasson

Table II Correlation coefficients of control values*

Parameter	Total blood volume index	Cardiac index	Heart rate	Stroke index	Central blood volume index	Mean transit time	Right atrial pressure	Brachial arterial pressure	Total systemic resistance
Total blood volume index		0 07	0 05	0 02	0 19	0 09	0 18	0 06	−0 09
Cardiac index			0 3	0 69	0 06	−0 77	−0.50	−0 4	−0 9
Heart rate				0 01	−0 19	−0 87	−0 31	0 21	−0 67
Stroke index					0 49	−0 22	−0 40	0 37	−0 47
Central blood volume index						0 57	−0 25	−0 13	−0 19
Mean transit time							0 3	−0 35	0 59
Right atrial pressure								0 08	0 60
Brachial arterial pressure									0 12

*Coefficients greater than 0 60 are underlined

Table III Correlation coefficients of changes after arteriotomy

Changes in	Total blood volume index	Cardiac index	Heart rate	Stroke index	Central blood volume index	Mean transit time	Right atrial pressure	Brachial arterial pressure	Total systemic resistance
Total blood volume index		0 42	0 13	0 34	0 05	−0 78	−0 32	−0 07	−0 40
Cardiac index			−0 06	0 63	0 19	−0 63	−0 26	0 08	−0 70
Heart rate				−0 68	−0 53	−0 30	−0 02	0 26	0 18
Stroke index					0 60	−0 04	−0 18	0 03	−0 43
Central blood volume index						0 58	−0 12	0 14	−0 06
Mean transit time							0 24	0 22	0 63
Right atrial pressure								0 22	0 41
Brachial arterial pressure									0 63

*Coefficients greater than 0 60 underlined

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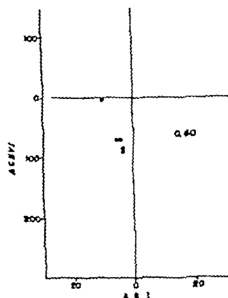


Fig 2 Relationship between the changes in stroke index and central blood volume per square meter

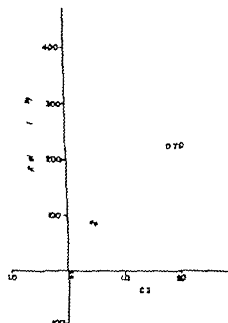


Fig 3 Relationship between the changes in cardiac index and systemic resistance

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Summary

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REFERENCES

1 Cournand A Riley R L Bradley S F Breed E S Noble R P Lauson H D Gregersen M I and Richards D W Studies of the circulation in clinical shock Surgery 13:964 1943

2 Schnabel T G Fitzpatrick H Thompson

a d Werkö L The effect of experimentally rdaced h pervol mia on cardiac function m normal jects and patients with mitral stero- J Clin Invest 38 11 1959
M Michael J and Sharpy Schafer E I Cardiac o tput in man by direct Fick method Effect of po ture enous pres ure change trepine and adrenaline Brit Heart J 6 33 1944
4 Warren J V Brannon E W Stead F A and Merrill A J The effect of enesection and the pooling f blood in the extrem ties on the trial pres ure nd cardiac output in normal subject w th observ tion on acute circulatory co lapse in three instances J Clin Inve t 21 33 194
5 Sherlin H A Chenev R H Govons S R, Hardy J D and Fletcher A G Jr On the diagnos of hemorrhage in man—a study of olunteers bled large amount Am J M Sc 208 421 1944
6 Remington J W Hamilton W F Caddell H M Boyd G H J ard Hamilton W F J Some circulatory responses t hemorrhage in the dog Am J Physiol 161 106 1950
Holt J P Effect of plethora and hemorrhage on left entricular olume and pres ure Circulation Res 5 2 3 1957
8 Guyton, A C Lindsey A W Kaufman B N and Abernathy J B Effect of blood trans fusion and hemorrhage on cardiac output and on the enous return curv Am J Physiol 194 263 1958
9 Sjöstrand T Volume d distribution of blood and their significance n regulating the circula tion Physiol Rev 33:202 1953
10 Wer ler V M Leonard J J and Warren J V Effects of posture nd atropine on the cardiac output J Clin Invest 36 1656 1957
11 Lilienfield L S nd Kovach R D Simplified method for calculating flow mean circulation time ar d dow lope from indicator-dilution curves Proc Soc Exper Biol & Med 91 595 19 6
1 Snedecor G W Stati tical methods Ames Iow 1956 Iow Stat College Press
13 Johnson S R The effect of some anaesthetic ents on the circulation in man Acta chir scandina Suppl 158 19 1
14 Cobb L A Ralston L A and Bruce R A Relation hips between stroke olume cardiac output and central blood olume in cardiac patients (Ab tract Cl Res 99 1959
15 Rapaport E Kuida H Haynes F W nd Dexter L The pulmonary bloc l olume in mitral tenosis J Clin Invest 35 1393 1956
16 Cobb L A Kramer R J and Finch C A Circulatory effects of chronic hypervolemia in pol cythemia era J Cl Invest 39 17 2 19 0
1 Hamilton W F The phy iology of the cardiac output (The Lewis A Connor Memorial Lecture) Circulatio 8 527 19 3

The effect of local pH changes on blood flow in the dog

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Alteration in the metabolism of an organ is well known to affect local blood flow. Variations in tissue metabolism can also induce changes in pH. It seemed of interest to us to determine how important pH variations themselves are for local blood flow. Although the subject is by no means new, we could find no satisfactory answers to this question. Early workers in this field using the Trendelenburg preparation in the frog, the isolated rabbit ear, and perfusion of the hind limb of the cat reported decreased blood flow after the administration of alkali. On the other hand, Kester and associates[1] and Deal and Green found increased blood flow in the femoral artery of the dog after local injection of either acid or alkali. These authors did not correct the ionic composition and osmolarity of their solutions to that of blood nor did they give any information of the effect of prolonged infusion of different buffer solutions.

The purpose of this study was to determine the effect of local pH changes on peripheral blood flow when buffers were given by infusion over prolonged period. Efforts were made to induce changes in local blood pH insufficient to provoke important systemic reactions, to avoid changes in osmolarity and concentration of sodium in the blood, and finally to obtain some information of the mechanism of action of acid and alkali on vessels.

Methods

Mongrel dogs weighing 8.0 to 17.4 kilograms and anesthetized with sodium pentobarbital (30 mg./Kg. intravenously plus 15 mg./Kg. intramuscularly) were used in these experiments. The glycine-alanine-phosphate buffers were adjusted to the desired pH and modified slightly so that at each pH they contained about 140 mEq. of sodium and of 330 milliosmol. After the administration of 4 mg./Kg. body weight of heparin sodium (1 mg. = 130 U.S.P. units), a needle was inserted into the femoral artery. Except where stated otherwise, buffers were infused through this needle at a rate of 4 ml. per minute. The sequence in which buffers at different pH's were administered was varied. Blood pH was determined by using a radiometer within 30 seconds of the withdrawal of blood samples. Blood flow in the majority of these experiments was determined by venous occlusion plethysmography. A plethysmograph of suitable size and composed of Plexiglass was placed around the hind limb above the knee of the dogs so that both muscle and skin vessel territory

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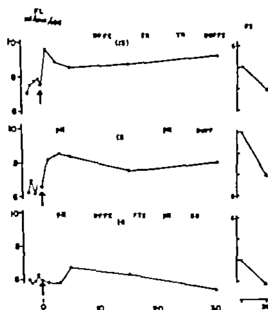


Fig 1 Effect of inf sion of pH 2 0 buffer on blood flow in the femoral rtery nd pH in the p-lateral femoral ein of the dog Control flows are represented by the poi t to the left of the rrow which marks the start of the inf sion The number of animals in each group is given in parentheses

were examined The plethysmograph was filled with air and sealed with insulating putty The outlet from the plethysmograph led to a high sensitivity Sanborn microphone A calibration system utilizing a 0 5 ml syringe was built into the tube leading from the plethysmograph to the microphone Records were obtained from a Sanborn Twin Viso Cardiette utilizing a Sanborn elertromanometer Paper speed was 25 mm per second Venous occlusion cuffs of different size depending on the size of the animal were inflated suddenly from a pressure reservoir For occlusion the pressure which gave the highest flow value for each animal was employed This was found to be preferable to utilizing an arbitrarily fixed pressure Blood flow was registered at least four times prior to each infusion then each minute for 5 minutes and at least three times at 5 minute intervals thereafter

In 6 experiments blood flow was measured by the method of Girling[4] in the femoral and carotid arteries This method utilizes a double cannulation of the artery The proximal cannula leads into a small chamber separated from an ink writing mercury manometer by a slack rubber membrane The distal cannula leads from this chamber back into the artery When the proximal plastic cannula is occluded for a short period (2 seconds in our experiments) the pressure in the manometer transmitted through the rubber membrane causes the blood in the chamber to flow into the distal artery at a rate dependent on the resistance in this artery The result is a fall in the pressure record proportional to the blood flow at the site of cannulation The blood flow can then be calculated from the magnitude of the pressure drop the cross sectional area of the manometer tube and the duration of the occlusion

In a further 7 experiments on dogs maintained by artificial respiration the effects of respiratory acidosis or alkalosis was studied These changes were produced by changing the stroke volume and rate of a Bodine respiratory pump

*Tygon Bury-Seal T nco Manufacturing C mpa y Canada

Results

In the first experiments attempts were made to introduce acid and alkali buffers in an amount sufficient to alter pH in the observed vascular area but insufficient to produce changes in blood pressure heart rate or respiratory rate in the animal In 3 dogs the intra arterial infusion of pH 2 0 or pH 12 0 buffers during a period of 90 minutes at the rate of 4 ml per minute caused little change in heart rate blood pressure or electrocardiogram although after infusion of acid buffer the pH in the ipsilateral femoral vein was reduced by at least 0 2 and after alkaline buffer it was increased by at least 0 2 Respiratory rate was slightly elevated by infusion of pH 2 0 buffer and decreased by infusion of pH 12 0 buffer However in a larger series of animals (26 dogs) respiratory rate after 30 minutes of infusion of these buffers was not materially affected

In 12 dogs the pH changes were registered simultaneously in both femoral veins during the intra arterial infusion of pH 2 0 and pH 12 0 buffers As expected pH changes on the side of the infused artery were consistently greater than in the contra lateral vein On the side of infusion acid buffer decreased the control blood pH by 0 27 whereas by only 0 09 in the contra

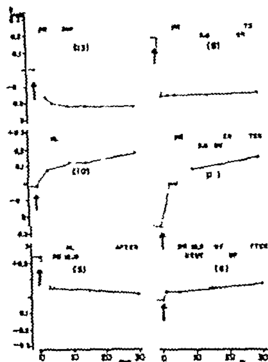


Fig 2 Alteration of femoral vein pH by the infusion of buffers of different pH in the ipsilateral femoral artery The start of infusion in each case is marked by an arrow The number of animals in each group is given in parentheses

lateral vein The corresponding effects of alkaline infusion were 0 31 and 0 07 These findings support the contention that the pH changes in our experiments could be considered as mainly local

The infusion of *pH 2 0 buffer*—which was of course markedly diluted in the vessels by blood—caused an increase in blood flow (Fig 1) When this was given after an infusion of a buffer adjusted to the individual control venous pH of the dogs (neutral buffer) the increase in blood flow was quite marked at the first minute of infusion When 4 ml per minute of acid buffer was infused into the femoral artery of 13 animals the increase in flow in the first minute was significant (t = 3 0 $p < 0.01$) As the infusion was continued the average blood flow was reduced but was still consistently elevated over the 30 minute test period No significant difference was found between the 1 and 15 minute values When pH 2 0 buffer was replaced by the neutral buffer flow returned to control levels in about 5 minutes In this group of dogs the average pH in the femoral vein on the side of the arterial infusion had decreased at the end of 30 minutes from 40 to 7 18 This alteration in blood pH was produced rather abruptly (Fig 2)

In 9 animals pH 2 0 buffer was infused at a rate of 1 8 or 16 ml per minute These variations in the rate of infusion caused correspondingly smaller or greater changes in blood pH and increases in flow Similarly when 4 ml per minute of *pH 3 0 buffer* was administered to 7 dogs the augmentation of blood flow was less than that caused by pH 2 0 buffer infused at the same rate under these circumstances the pH in the corresponding femoral vein was reduced from an average of 7 42 to 7 22 Indeed in this small series the increase in flow was not significant in the first minute and in the fifth minute of infusion t was 2 50 ($p = 0.02$ to 0.05) It is notable that injection of buffers into the femoral artery at acid or alkaline pH s when tested in 3 dogs with Girling s method gave increases in flow when expressed in maximal effect quite similar to those reported by Kester and associates[4]

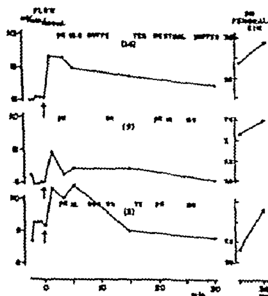


Fig 3 Effect of infusions of pH 12 0 buffer on blood flow in the femoral artery and pH in the ipsilateral femoral vein of the dog Control flow are represented by the points to the *left* of the arrow which marks the start of the infusions. The number of animals in each group is given in parentheses

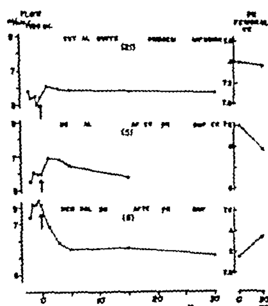


Fig. 4. Effect of infusion of neutral buffer on blood flow in the femoral artery and pH in the ipsilateral femoral vein of the dog. C and 0 [illegible] represent [illegible] by the point at the left of the arrow which marks the start of the infusion. The number of animals in each group is given in parentheses.

However, the average increase in flow by Girling's method was considerably less.

To obtain information on the mode of action of acid on blood flow the sequence in which infusions were given was varied. In 8 animals pH 2.0 buffer infused immediately after the infusion of pH 12.0 buffer caused a marked increase in blood flow (Fig. 3). Similarly, although less obvious in the first minute, the infusion of this buffer in 6 dogs was still effective after the previous administration of pH 3.0 buffer. On the other hand, infusion of pH 3.0 buffer, which was effective before pH 2.0 infusion, caused no increase in blood flow when it was given in the same dogs after 60 minutes of infusion of pH 2.0 buffer.

The infusion of *pH 12.0 buffer* after the administration of neutral buffer increased the blood flow. This augmentation in a group of 14 dogs (Fig. 3) was rather consistent and quite marked in the first minute ($t = 2.56$, $p < 0.01$). However, in contrast to infusion of acid, with continued infusion of alkaline buffer the blood flow was gradually reduced in most cases. After 15 minutes the increase in flow was no longer significant as compared to control values. Indeed, in 5 animals in which infusion was continued over a period of 1 hour, average blood flow was lower at the end of this infusion than in the control period. Blood pH in the femoral vein on the infused side increased at the end of 30 minutes of infusion from 7.37 to 7.56. Repeated determinations of blood pH during the infusion in 10 dogs is shown in Fig. 2.

Infusion of *pH 10.0 buffer* to 11 dogs increased blood flow only slightly and blood pH from 7.36 to 7.47. Indeed, the increase in blood flow was not significant after 1 minute and the average flow was still lower after 15 minutes of infusion.

Buffer of pH 12.0 caused an increase in flow in 5 dogs in which infusion followed the administration of pH 2.0 buffer and also in 3 other dogs in which the infusion followed that of pH 10.0 buffer. On the other hand, pH 10.0 buffer in 5 animals increased flow after neutral buffer but decreased blood flow when it was given after pH 12 buffer.

Neutral buffer was adjusted in each case to the control venous pH of the dogs as determined at the beginning of the experiments. In 21 dogs neutral buffer caused only an insignificant increase in flow (Fig. 4). This elevation of blood flow could be explained by the extra volume added to the femoral flow by the infusion of 4 ml. of fluid per minute. The augmentation in flow produced by neutral buffer after infusion of pH 12.0 buffer was not statistically significant. On the other hand, after pH 2.0 buffer, flow was markedly reduced in 5 out of 6 dogs in the first minute after the infusion of neutral buffer (Fig. 4).

To determine how pertinent these results would be when applied to another vascular territory, blood flow was measured during 15 minutes of infusion of pH 2.0 and pH 12.0 buffers into the common carotid artery about 5 cm. below the arterial bifurcation. For the sake of comparison, blood flow was also obtained in the femoral artery by the method of Girling using double cannulation. Blood flow was increased less in the carotid artery than in the femoral artery during the infusion of acid or alkaline buffer; however, the difference between the responses in the two arteries was not significant. The method of Girling registers

not only flow but also pressure in the cannulated artery. From experiments using this method we learned that the local arterial pressure (femoral or carotid) was slightly but consistently decreased during infusion of acid or alkali. As a consequence peripheral resistance was more decreased by the infusions than was indicated by the increases in flow alone.

The role of the *nervous system* in the vascular response to acid and alkaline buffers was studied in additional animals. In 7 dogs the effect of infusion of pH 2.0 and 12.0 buffers into the femoral artery was studied before and after acute denervation. While the dog's leg remained in the plethysmograph and the needle in the femoral artery, the sciatic and femoral nerves were sectioned and a periarterial denervation was performed. No differences were observed in the increases in flow caused by alkaline buffer before or after denervation. However, acid buffers failed to cause increases in flow in 5 out of 7 dogs after acute denervation. Because of the surgical manipulation necessary in this preparation, we were somewhat skeptical of the reliability of the flow values. Therefore in 5 dogs we investigated the effect of pharmacologic inhibition of the sympathetic and parasympathetic innervation on the above described vascular responses. The increase in blood flow produced by pH 2.0 and pH 12.0 buffer was unaffected by the previous and simultaneous intra-arterial administration of 0.1 mg per minute of atropine. However, pH 2.0 buffer caused less increase in flow after bretylium tosylate was given in a dose of 3 mg/kg intravenously. This effect in each of the 5 dogs was more pronounced at 90 minutes than at 30 minutes after the injection of bretylium tosylate, when the sympathetic nerve ends are known to be already markedly inhibited. On the other hand, in the same animals no consistent effect of bretylium tosylate was observed on the increase in blood flow caused by pH 12.0 buffer.

The effect of *respiratory* alkalosis or acidosis on the blood flow is by no means identical with that of the above-described metabolic alkalosis and acidosis. When venous pH was increased by at least 0.1 after 15 minutes of hyperventilation, blood flow in the hind limb decreased in each of 5 dogs. A decrease in pH of at least 0.1 produced by hypoventilation had a less consistent effect on blood flow.

Discussion

These experiments were designed to study the effect of infusions of acid and alkali on blood flow while avoiding the influence that these infusions might have on flow as a result of changes in osmolarity or in sodium gradient. Under these circumstances the administration both of acid and of alkali increased blood flow in the femoral artery. A similar but less pronounced effect of these infusions was observed in the carotid artery. These results in principle are in agreement with those of Kester and associates, Deal and Green's results[4] in the femoral artery, and the findings of McElroy and associates in the coronary artery.

Since the pH of the blood is a very stable value, it was necessary to administer large volumes of the different buffer solutions in order to alter the blood pH. It is necessary, therefore, to consider the effect of the fluid volume itself in the interpretation of these results. In 3 dogs in which the effect of infusion of these large volumes on blood pressure, heart rate, and electrocardiogram was studied, no important alteration was observed in these parameters. Edema in the infused leg, even after infusions which lasted for several hours, was observed only rarely. Furthermore, the sequence of administration of the different buffers was varied in different animals so that interference as a result of expansion in plasma volume was minimized.

There was a direct relationship between the change from control blood pH produced by the different types of infusions and the increase in blood flow. The pH 2.0 buffer was more effective in increasing blood flow than the pH 3.0 buffer, and pH 12.0 buffer was more effective than pH 10.0 buffer. Similarly, neutral buffer was ineffective. These experiments indicate that it is the alteration from the neutral pH and not the absolute pH difference which is the trigger for an increase in flow. If this were not the case, then pH 12 given after pH 2.0 buffer, or pH 2.0 after pH 12.0 buffer, would have had greater effect than was observed pH 3.0 after pH 2.0 or pH 1

pH 12.0 buffer would have elevated ... did not decrease it, and neutral buffer after pH ... 0 buffer would not decrease the flow.

Both acid and alkaline buffers reduced peripheral resistance. However, we believe that this does not mean that these two antagonists act in the same way on the vessel. The injection of acid caused a more prolonged increase in flow than did the injection of alkali. The increase in blood flow after alkaline infusion was gradually decreased while the infusion was continued, whereas the pH increase in blood was at least as great during the later stages of infusion as earlier. Acid infusion, on the other hand, had sustained action. Furthermore, pH 2.0 buffer after pH 12.0 buffer and pH 12.0 buffer after pH 2.0 buffer still had marked effect. The results after acute denervation or after the administration of bretylium tosylate also suggest a difference between the mechanisms of action of acid and alkali. This difference might be explained by a better adaptation of vessel to alkalosis than to acidosis. In the effect of acid it seems probable from these experiments that the sympathetic nervous system is also involved. Whether the response of vessels to pH is secondary to changes in the blood pH, tissue pH, or pH gradient is unknown and must await further experimentation.

Respiratory alkalosis had an effect on blood flow opposite to that of metabolic alkalosis. These results correspond to those found recently by Patel and Gowdey[8] and could be explained by a depression in blood pressure during artificial hyperventilation.

Summary

Acid and alkaline buffers were administered by intra-arterial infusion at different pH's to dogs. Blood flow was measured with venous occlusion plethysmography and in a few cases by arterial cannulation. Infusions were given affecting mostly the local pH insufficient to cause major systemic reactions.

Both acid and alkali significantly increased blood flow in the femoral artery. This effect was less pronounced in the carotid artery.

When the sequence of the different buffers was varied, the response suggested that the difference from the control blood pH of the animal rather than the absolute differences was the factor causing increases in flow.

The sustained and more prolonged effect of acid infusion, the difference after denervation, and other results suggest different mechanisms for the action of acid and alkali on the vessel.

REFERENCES

1. Snyder, C. D., and Campbell, B. A.: Vascular reaction to epinephrine in perfusates of various hydrogen ion concentration, Am. J. Physiol. 51:199, 1920.
2. Atzler, E., and Lehmann, G.: Dependence of the contractile reaction of the peripheral vessels upon the hydrogen ion concentration of the perfusion fluid, Pflüger Arch. ges. Physiol. 205:578, 1924.
3. Hemingway, A.: The sensitizing action of alkalies, J. Physiol. 62:81, 1926.
4. Kester, N. C., Richardson, A. W., and Green, H. D.: Effect of controlled hydrogen ion concentration on peripheral vascular tone and blood flow in innervated hind leg of the dog, Am. J. Physiol. 169:678, 1952.
5. Deal, C. P., and Green, H. D.: Effect of pH on blood flow and peripheral resistance in muscular and cutaneous vascular bed in hind limb of pentobarbitalized dog, Circulation Res. 2:148, 1954.
6. Gerling, F.: Effect of intravenous and intra-arterial adrenaline and of adrenaline after Priscoline on hind limb of intact rabbit, Am. J. Physiol. 161:100, 1956.
7. McElroy, W. T., Jr., Gerdes, A. J., and Brown, E. B., Jr.: Effect of CO_2, bicarbonate and pH on the performance of isolated perfused guinea pig hearts, Am. J. Physiol. 195:412, 1958.
8. Patel, Y. F., and Gowdey, C. W.: Changes in responses to catecholamines with changes in ventilation, Canadian Federation of Biological Societies, Third Annual Meeting, Winnipeg, 1960.

Monocusp aortic valvular prosthesis in dogs

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For diseased calcified stenotic or insufficient aortic valves, replacement of one cusp with a prosthesis may bring a great improvement of hemodynamics. Total replacement may be the final goal, but substitution of only one leaflet is easier and the results obtained may project some light on the problems that will be encountered with total replacement of the valve. This report describes the replacement in dogs of the noncoronary cusp of the aortic valve with a prosthetic cusp.

Materials and preparation of valves

The materials used were knitted Teflon, polyurethane, Silastic (silicone rubber), and collagen with Dacron mesh. The monocusp valves were made on semilunar tricusped molds patterned from a dog's aortic valve. In making Teflon† and collagen† cusps, a small piece of the material was held between a male and female mold and cut out along the edge of the mold. Polyurethane† and Silastic† valves were made by dipping open molds in solutions of the plastic. The insertion lines of the valves were reinforced with braided Elgiloy† wire frames with 5 or 7 eyes; the Teflon valves were strengthened with a thick Teflon thread and the collagen, polyurethane, and Silastic valves with a thick Dacron thread. Polyurethane valves were siliconized with Siliclad† after the insertion lines were covered with polyurethane sponge. The insertion lines of Silastic valves were glued to Ivalon sponge by using a room temperature vulcanizing Silastic†. These sponges serve for the ingrowth of fibrous tissues and prevent regurgitation around the valves. In order to reduce the time of insertion of the valve, 5 to 7 Mersilene 3-0 sutures (with double needles†) were attached to the insertion lines of the valves beforehand (Fig. 1) and were sterilized together with the valves in an ethylene-oxide sterilizer.

Methods

Twenty-three mongrel dogs, 19.4 to 28.9 kilograms in weight, were anesthetized with Nembutal. During the operation the circulation was maintained extracorporeally by a Foregger pulsapirator.† The chest was opened through the fourth right intercostal space. The incision of the aortic wall was

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*The first monocusp valves in our laboratory were made by Dr. M. [illegible] in 1958.

†Teflon: United States Catheter and Instrument Corp., Glens Falls, N. Y. Collagen: Ethicon, Inc., Somerville, N. J. Polyurethane: B. F. Goodrich Co., Akron, Ohio (polyurethane V. C. [illegible]). Silastic: Dow Corning Corp., Midland, Mich. (Silastic [illegible]). Elgiloy wire frames: Elgin National Watch Co., Elgin, Ill. Ivalon: Clay-Adams, Inc., New York, N. Y. Vulcanizing Silastic: Dow Corning Corp., Midland, Mich. Double-armed Ethicon sutures, Somerville, N. J. (34 inches — Dacron). Pulsator: Foregger Co., Inc., Roslyn Heights, N. Y.

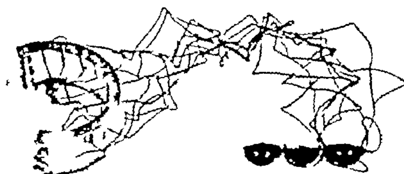


Fig. 1. M[illegible] u p[illegible] rtic [illegible] made of polyurethane. A strip of polyurethane pr[illegible] glued along the [illegible] on the extracular side. In the right [illegible] tures with double needles re [illegible] hed [illegible] t. The ends of the utures are sep[illegible]ly fixed in ten[illegible] on the horseshoe ring (left) so that they [illegible] not become entangled.

somewhat curved, the lower end was stopped above the commissure between the posterior and right leaflets in order to prevent constriction of the noncoronary sinus by duplication in the suture line of the aortic wall. After the noncoronary cusp was excised, the artificial cusp was put in place. The sutures previously attached to the valve were brought to the outside of the aorta and tied there over a piece of Teflon felt (Fig. 2). In the first four experiments aortic stenosis was created by sewing the right and the left natural leaflets together.

In order to prevent the formation of thrombus on the valve or to dissolve thrombi which might already exist, the following drugs were given to some dogs either separately or in combination: intravenous injections of 2,000 units of fibrinolysin per kilogram of body weight each day for 4 days; subcutaneous injections of 3.5 mg./Kg. of lipoheparin every 8 hours for 7 days; 300 mg. of nicotinic acid per day.

Ten cineangiocardiograms[*] have been taken in 9 dogs between 5 and 75 days after operation.

Results

Smooth polyurethane, Silastic, collagen with Dacron mesh, and knitted Teflon valves were put in 16, 2, 2, and 3 dogs, respectively (Table I).

[*]Angiocardiograms were made by Dr. [illegible] in the cardiovascular laboratory at the Cleveland Clinic.

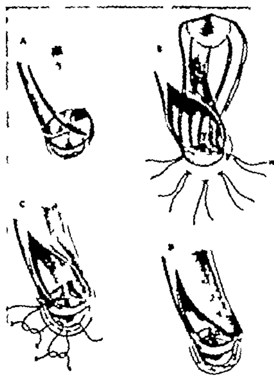


Fig. 2. Insertion technique of the monocusp valve. A, Incision of aortic wall. Note that the lower one third of the incision is curved, pointing to the commissure between the right and the posterior leaflet. B, All sutures are passing out of the aorta along the bottom of the posterior leaflet, which has been removed. C, Fixation of the valve start from the commissure between the left and posterior leaflets outside the aorta by tying the sutures over a piece of Teflon felt. D, Fixation of the valve is completed.



Fig 3 Smooth polyurethane monocusp in the dog sacrificed 130 days after operation Note that the fixation of the valve is completely covered with endothelium which shows no sign of growing over the leaflets

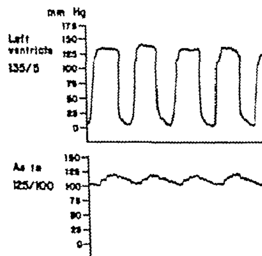


Fig 4 Pressure tracings in the left ventricle and in the aorta after implantation of an artificial monocusp and creation of stenosis by sewing together the two remaining natural leaflets Note that the postoperative pressure gradient across the aortic valve is 10 mm Hg

One of 2 dogs with a Silastic valve survived 4 days before dying of aortic insufficiency caused by a tear along the fixation line of the valve extending to the bottom of the leaflet The other died of occlusion of the left coronary ostium 4 days after operation The sinus of the artificial leaflet was filled with thrombi This corroborates earlier experience that Silastic is too weak to make thin leaflets and that it forms no safeguard against thrombosis

One of 2 dogs with a collagen valve survived 15 days but died of subacute endocarditis the collagen cusp was collapsed and filled with thrombi The other is alive 165 days after operation In the angiocardiogram taken 45 days postoperatively the collagen cusp proved to be working although a small amount of regurgitation was observed

In 2 dogs with knitted Teflon valves which survived 11 and 23 days respectively no thrombus was found However the Teflon cusp was shrunken covered with fibrin and in Dog No 13 adhered to the right natural leaflet This supports our previous experience with Teflon both in





Fig 5 Cineangiocardiogram of one dog taken 11 days after operation in which the two remaining natural leaflets were sewn together after an artificial monocusp was put in place A The braided Elgiloy frame of the artificial valve B The sinus of the artificial cusp filled with dye

experimental patches and in mitral valves which indicates that this material will develop a layer of fibrin which disrupts or leads to the healing or growing together of the ... Later fibrosis occurs in the spaces between the Teflon fibers and the valve flaps.

Thirteen dogs with polyurethane monocusp valves survived longer than 2 days. 3 dogs are alive from 90 to 126 days, one of which has a thrombus according to the cineangiocardiogram. 10 died or were sacrificed. The polyurethane cusp was found to be filled with thrombus in 6 of the dogs. In all 3 dogs treated with fibrinolysin only thrombosis was found. In the one dog treated with fibrinolysin, heparin, and nicotinic acid and subsequently sacrificed 13

Table I. Monocusp aortic valve prostheses in dogs

Experiment number	Body weight of dog (Kg.)	Material	Edge: Reinforcement	Edge: Covering	Silicone coating	Cardiac arrest (min.)	Fibrinolysin	Heparin
1	25	Smooth PU†	Braided Elgiloy wire	PU sponge	+	16		
2	2	Smooth PU	Braided Elgiloy wire	PU sponge	+	20		
3	23	Smooth PU	Braided Elgiloy wire	PU sponge	+	31		
4	27	Smooth PU	Braided Elgiloy wire	PU sponge	+	23		
5	28	Smooth PU	Braided Elgiloy wire	PU sponge	+	19		
6	29	Smooth PU	Braided Elgiloy wire	PU sponge	+	18		
7	22	Smooth PU	Mersilene thread	PU sponge	+	19	+	+
8	21	Silastic	Mersilene thread	Ivalon sponge	−	20	+	+
9	24	Silastic		Ivalon sponge	−	21	+	
10	2	Collagen	Teflon thread		−	20	+	
11	25	Collagen	Teflon thread		−	18		
12	26	Knitted Teflon	Braided Elgiloy wire		−	23		
13	2	Knitted Teflon	Teflon thread		−	28		
14	22	Knitted Teflon	Teflon thread		−	13		
15	22	Smooth PU	Mersilene thread	PU sponge	+	21	+	
16	23	Smooth PU	Braided Elgiloy wire	PU sponge	+	23	+	
17	23	Smooth PU	Braided Elgiloy wire	PU sponge	+	2	+	
18	20	Smooth PU	Mersilene thread	PU sponge	+	21	+	
19	26	Smooth PU	Mersilene thread	PU sponge	+	30		
20	24	Smooth PU	Mersilene thread	PU + BH	−	28		
21	23	Smooth PU	Mersilene thread	PU + BH	−	32		
22	23	Smooth PU	Mersilene thread	PU + BH	−	7		
23	22	Smooth PU	Braided Elgiloy wire	PU + BH	−	23		

Aortic stenosis was produced by sewing the two remaining natural leaflets together.
†PU: Polyurethane. Commercial sponge lined with polyurethane V.C. (Estane, Goodrich).
‡BH: Barium heparin. This was used to prevent the formation of thrombus along the fixation line of the artificial monocusp. The ratio ...
Ivalon—polyvinyl alcohol, Clay Adams, Inc., New York, N.Y.

days after operation there was no thrombus in the sinus of the polyurethane cusp

The overall results indicated a high incidence of thrombosis in at least 7 of the 13 cases

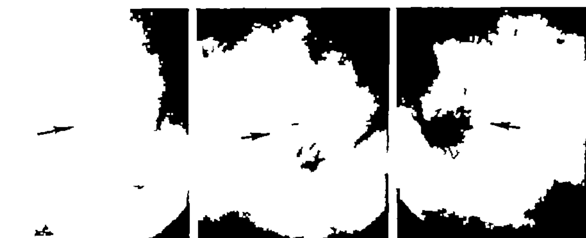
In 2 dogs (Nos 2 and 18 sacrificed 130 and 82 days after operation respectively) the valve fixation line on the ventricular side was completely covered with endothelium which did not grow over to the polyurethane leaflet (Fig. 3) Thus no problem exists with smooth valve leaflets on the exposed high flow side of the valve leaflet

It has often been noticed in a valve testing machine[4] that a leaflet stiffer than the other two does not move at all The same thing may happen when the one

Table I Monocusp aortic valvular prosthesis in dogs—Cont'd

Survived (days)	*Autopsy result*		*Cause of death*
	Artificial cusp	*Other parts*	
1	Leaflet too short	Pulmonary edema	Pulmonary edema
130	Filled with thrombus		Sacrificed
1/6	I place and II right		Myocardial damage
10	Filled with thrombus	Extensive intestinal necrosis due to mesenteric thrombosis	Peritonitis
8	Big thrombus	Saddle embolus in abdominal aorta	Multiple emboli
2	Big thrombus	500 ml. of bloody fluid in the chest	Bleeding in the chest
13	No thrombus	750 ml. of blood in the chest	Sacrificed
4	Leaflet torn no thrombus	Pulmonary edema	Pulmonary edema
4	Filled with thrombus	One infarct in spleen	Occlusion of left coronary ostium with thrombus
15	Filled with thrombus	Pulmonary edema	Pulmonary edema
165 (alive)			Cineangiocardiogram no thrombus cusp shrunk somewhat
2	Collapsed and shrunken		Bleeding in the chest
11	Adherent to right natural leaflet	Right natural leaflet damaged	Aortic stenosis and insufficiency
23	Covered with thick fibrin no thrombus		Myocarditis
11	Filled with thrombus	T aortic natural leaflets damaged	Endocarditis
84	Filled with thrombus	Kidney full of infarcts saddle embolus in aorta	Multiple emboli
124 (alive)			Cineangiocardiogram thrombus in cusp
82	Filled with thrombus		Sacrificed
1/6	I place	Abdominal cavity full of bloody fluid	Transfusion reaction
18	Filled with thrombus	Sutures for stenosis broken aortic insufficiency	Pulmonary edema
93 (alive)			Cineangiocardiogram no thrombus in artificial cusp
90 (alive)			Cineangiocardiogram no thrombus in artificial cusp
31	Thin thrombus along the insertion line no more than desirable	Two natural aortic leaflets covered with thrombi extensive intestinal necrosis due to mesenteric thrombosis	Peritonitis

of barium impure and polyurethane V C unit 1 (Organon Bath rlands)



F . 6 C re   rd   m (Do N   (T bl I) made 90 d   fter sert   f monocu p al   I sewn together (he remaining nat   l d   k fl t The artifi l (monocusp arrows) p (*ed*   *ed by*   *o*) filled w h   med um nd   leaflets t are mobile

artificial monocusp leaflet is stiffer than the two remaining natural leaflets. The lack of movement may promote the formation of thrombus under the artificial leaflet. In patients with aortic stenosis the rigid calcified leaflets are not movable. The artificial leaflet therefore has to move, and as a result the formation of thrombus may be prevented. In the last 4 dogs, stenosis was artificially produced by sewing the right and left leaflets together. A postoperative pressure gradient measured across the aortic valve in one such dog was 10 mm. Hg (Fig. 4).

A cineangiocardiogram taken 11 days after operation in one dog showed that the polyurethane cusp was moving (Fig. 5). The dog died 31 days postoperatively, and at autopsy an extremely thin thrombus was noticed firmly adhering along the insertion line of the polyurethane cusp. The sutured natural leaflets, on the other hand, were covered with irregular mushroom-like thrombi which presumably led to mesenteric embolization and death. The other dogs with the natural valve leaflets sewn together (Nos. 21 and 22, Table I) were more fortunate. Cineangiocardiograms made more than 90 days after insertion of the artificial cusps showed them to be free of thrombus (Fig. 6).

Discussion

Materials used in the experiments are conveniently divided into two categories: rough (collagen and Teflon) and smooth (Silastic and polyurethane). Collagen is the only material that is not only water repellent but even water absorbent. It is well accepted and pliable but weak. The collagen provided by Ethicon is reinforced with Dacron mesh. Collagen with a finer Dacron mesh than that used in our experiments might be tried. Although our experiences with collagen inserts in the atria showed extensive thrombosis. Teflon is inert and strong; nevertheless it is not recommended as a material for artificial heart valves because it is inevitably covered with fibrin which becomes increasingly thicker. The fibrin finally makes the leaflet stiff or forms pseudoleaflets. In an autopsy of one of our experiments we saw the Teflon leaflets grown together with the natural leaflets. These observations correspond with our experimental results in dogs having plastic patches in the heart chambers and in dogs with artificial mitral valves. The water repellent property of Silastic is advantageous, but because it has a tendency to tear under the high pressures in the left side of the heart, it is not recommended as a material in the making of artificial heart valves. If it were used, it should have a skeleton of a stronger material, such as Dacron mesh. Silastic, even if it did not tear, is no safeguard against the formation of thrombosis. Polyurethane, mentioned in another published paper,[1] is strong and can be siliconized

to make it more water repellent. In spite of our hopes, polyurethane leaflets would not stay open. Thrombi nearly always are formed in the sinus and originate from the insertion line of the artificial cusp. Since we forced the artificial leaflet to move by sewing the right and the left leaflets together, less thrombus was formed in the sinus of the artificial cusps.

The incision of the aortic wall in the earlier work was straight; it extended down into the middle of the noncoronary valvular sinus. This led to a reduction of the concerned sinus and a distortion of the inserted artificial valve. Presently, the aortic incision is curved, pointing at the commissure between the posterior and right leaflets. It does not enter the sinus proper, yet gives a sufficient view of the operative field. If the sutures on the outside of the aorta are tied over thick Teflon felt, valve cusps without a rigid frame are not distorted.

Administration of fibrinolysin alone to 6 dogs did not dissolve thrombi formed on the fixation line of the artificial valve cusp. A combination of fibrinolysin and heparin seemed beneficial in one dog (No. 7) which showed no thrombus after 13 days. The experiment was inconclusive in another dog because, although there was no thrombus, the Silastic leaflet tore after 4 days (No. 8).

Conclusions

(1) Artificial monocusp aortic valves made of collagen, Teflon, Silastic, and smooth polyurethane were put into 23 dogs. (2) At first, the formation of thrombus or fibrin adhesion was noted in 14 dogs which survived longer than 2 days. Thrombosis occurred no matter what material was used, but not in 2 dogs which were treated with fibrinolysin and heparin. (3) Formation of thrombus originated from the insertion line of the artificial cusp in the sinus. (4) Cutting into the sinus proper can be avoided. (5) Rough materials promoted formation of fibrin on the cusps; smooth materials were better.

REFERENCES

1. Akutsu, T., Dreyer, B., and Kolff, W. J.: Polyurethane artificial heart valves in animals, J. Appl. Physiol. 14: 1045, 1959.
2. Mirkovitch, V., Akutsu, T., and Kolff, W. J.: Study of intracardiac thrombosis using plastic materials (Abstract), Physiologist 3: 114, 1960.
3. Kolff, W. J., Seidel, W., Akutsu, T., Mirkovitch, V., and Hardberg, J. P.: Rules for intracardiac thrombosis, Conference on Prosthetic Valves for Cardiac Surgery, Chicago, Sept. 9 and 10, 1960.
4. Mirkovitch, V., Akutsu, T., and Kolff, W. J.: Study of intracardiac thrombosis on plastics. Preliminary to the construction of artificial valves, J. Appl. Physiol. (Accepted for publication.)
5. Dreyer, B., Akutsu, T., and Kolff, W. J.: Testing of artificial heart valves, J. Appl. Physiol. 14: 476, 1959.

A study of arterial pressure plethysmograms and impedance plethysmograms

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In a previous communication in this Journal[1] comparison was made between intra-arterial pressure pulses and pulses obtained from the same artery and site through a cutaneously applied cuff, short rigid tube, and strain gauge. It was observed that whereas the intra-arterial pulse is not affected by extensive changes in applied cuff pressure, the pulse recorded through the cuff becomes larger, usually up to systolic levels, and its contour is altered at the various cuff pressures.[1]

With the means at our disposal at that time no further comparison between the contours of the intra-arterially and extra-arterially recorded pulses could be made. It became apparent that this could be done only by a continuous plotting of the two pulse values against each other (e.g., through a subtracting amplifier) if the pulses to be compared were made exactly equal in size. This would further indicate the nature of oscillometric arterial pulsations as obtained with a variety of cuff systems used in clinical medicine today.

In addition, pulses recorded with the cuff and strain gauge (hereafter called *pressure plethysmograms*) have been compared to pulses recorded by amplifying impedance changes of the artery under study. Comparison of the data from these two methods would indicate the nature of pressure and impedance plethysmograms and their differences from pressure pulses of the same artery.

Subjects and methods

Fifteen healthy young males were studied under the same conditions described in the preceding paper;[1] in addition, 8 men with various cardiovascular disorders were similarly studied. All experiments were performed on the brachial artery, and the arm was held at the cardiac zero level. Pressure pulses were recorded as reported in the preceding paper.[1] Pressure plethysmograms from the same artery were obtained by placing a small cuff on the skin exactly over the tip of the needle and connecting it with a 15 cm. long PE 280 tube to another P23AA gauge. The air in the system could be subjected to any desired pressure up to 300 mm. Hg. The output of the gauge was fed into a transistorized DC amplifier with a capacitor at its exit so that its time constant was 1.8 seconds when connected to the Electronics for Medicine recorder; the natural frequency response of the plethysmographic amplifier was well over 100 cycles per second.

The pulses were made equal in size by adjusting the gain of the plethysmographic amplifier. They were then fed into the subtracting amplifier,[1] the pressure pulse

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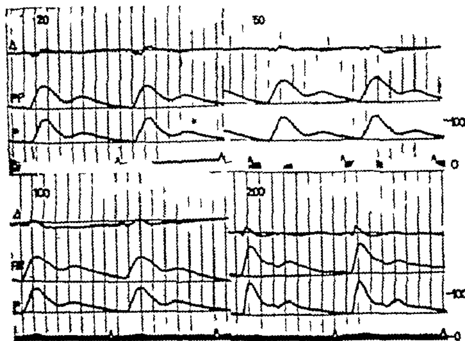


Fig 1 In each section from below upward intra arterial pressure base line electrocardiographic Lead II left brachial arterial pres ure (P) left brachial arterial pressure pleth smogram (P P equalized in height to the intra arterial pressure) obtained ex actly over the tip of the Cournand needle The top curve (Δ) the in_tantaneous dif ference bet een pressure (positi) and pres ure plethysmogram (negati) The numbers in each section ndicate the pplied cuff pressures in mm Hg nd t the right ar the calibration levels for the intra arterial pressure Time lines in 0 1 second Obser the constant difference in onset of the t pulses and the hanges in pulse contours ith the highest pplied pressure (200 mm Hg)

as positive input and the pressure plethys mogram as negative input The resultant subtraction curve was recorded along with the original pulses and ECG Lead II

Arterial impedance (volume) pulses were recorded between the Cournand needle and a subcutaneous electrode close to the tip of the intra arterial needle or between two subcutaneous electrodes inserted on either side of the artery In both cases the external cuff was positioned exactly over the impedance recording electrodes the sub cutaneous electrodes were insulated except for their tips The impedance amplifier was the same I arks unit employed in the preceding study [3] The size of the impedance pulse was adjusted to equal exactly that of the pressure plethysmogram The two pulses were fed into the subt acting am plifier but with the pressu e plethysmo gram as positive and the impedance pulse as a negative input Recording of the pulses and their difference was done on the same multiple beam recorder as reported above

Results

1 P essu e plethysmograms versus intra arterial pressure pulses The pressure ple thysmograms preceded the corresponding intra arterial pressure pulses by a varying interval constant in each case with normal sinus rhythm and under esting conditions The subtraction curves were composed therefore of an early negative positive deflection representing the difference in arrival times of the fronts of the pressure plethysmog am and of the intra arterial pressure pulse (Fig 1 all four sections) Similar precedence of the impedance pulse with respect to the pressure pulse was described in the preceding paper

In about two thirds of the cases the subsequent course of the pressure plethys mogram obtained with very low cuff pres su es (5 to 20 mm Hg) was identical with the intra arterial pressure pulse (Fig 1 upper left) thus the subtraction curve returned to its original base line after early biphasic swing In the other

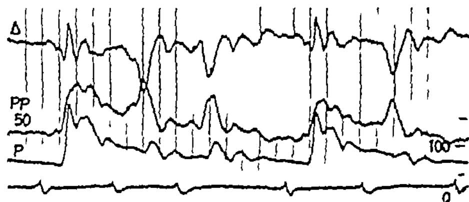


Fig. 2. As Fig. 1 but electrocardiographic Lead I from a young man with mitral disease, atrial fibrillation, and irregular ventricular rate. Observe the unequal height of the pressure plethysmogram compared to that of the intra-arterial pulses and the variable transmission times of the pulse.

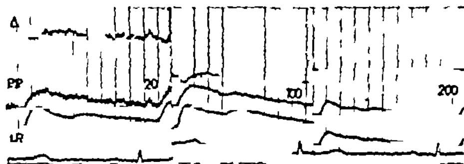


Fig. 3. From below upward: electrocardiographic Lead II, impedance plethysmogram (I.P.) of the left brachial artery recorded between subcutaneous needles on either side of the artery, pressure plethysmogram (P.P.) of the same artery recorded with the cuff over the subcutaneous electrodes, and subtraction curve (Δ) of the pressure plethysmogram minus impedance plethysmogram. The numbers indicate the applied cuff pressure in mm. Hg and the size of the pulses has been adjusted each time to make them exactly equal.

pressure plethysmograms exceeded in relative size the intra-arterial pressure pulse throughout most of the cycle, so that the subtraction curve returned below its original base line after the initial deflection. Higher cuff pressures increased the size of the pressure plethysmogram, and to make it equal to the intra-arterial pressure pulse the gain had to be progressively reduced. Without exception all such height-adjusted pressure plethysmograms exceeded in relative area the corresponding pressure pulses so that the subtraction curves remained below the original base line for the most part of each cycle after the early negative-positive swing. This is exactly the relation obtained by a comparison of height-equalized impedance arterial pulses with intra-arterial pressure pulses described in the preceding paper.[8]

Cuff pressures exceeding 100 mm. Hg partially impede the flow of blood at the recording site, the intra-arterial pulse becomes distorted with increased pulse pressure and faster upstroke and downstroke like a peripheral pulse (Fig. 1, lower right); despite this, the relation of the plethysmogram to intra-arterial pressure is the same as with lower cuff pressures.

During extrasystolic arrhythmias the pressure plethysmograms precede by varying distances the corresponding intra-arterial pressure pulses. Furthermore, the described constant relations of pulse sizes are disturbed, and marked beat-to-beat variation is observed. Multiple observa-

tions as the one in Fig 2 have indicated that the relative height of the pressure plethysmogram with respect to the intra-arterial pressure pulse increases with increasing diastolic pressure at the time of the ectopic beat Similarly the difference in onset of the two pulses seems directly related to the existing intra-arterial pressure Such observations suggest that the pressure plethysmograms are records of changes in diameter which may or may not be accompanied by perceptible changes in intraluminal pressure during similar disturbances of the cardiac rhythm

2 Pressure plethysmograms versus impedance arterial pulses In contrast to the above mentioned variable relations no major differences in contour between arterial impedance pulses and pressure plethysmograms have been observed the only noteworthy difference was a relatively faster rise (not onset) of the impedance pulse in most cases Apart from this there was no trend in the minor differences in contour encountered over the wide range of cuff pressures tested per individual Fig 3 indicates the differences in contour between the impedance plethysmogram and the pressure plethysmogram of the same brachial artery when the cuff pressure was raised from 20 to 200 mm Hg

Fig 4 further emphasizes the essential similarity of the two pulses it was obtained from a young man with mitral disease and atrial fibrillation and the ventricular rate varied widely from beat to beat despite the remarkable variability in pulse rate size and contour the recorded pulses with the two methods are almost identical and the slight differences were not accentuated when the cuff pressure was raised from 50 to 150 mm Hg

Discussion

The nature of the tracings obtained by pressure plethysmographic techniques is a subject of both theoretical and practical interest Such techniques have been used since the early years of this century (see the review by Frey[4]) and are still widely used in oscillometry today It should be known therefore whether the recorded pulsations bear any similarity to the variations in intramural pressure or to transverse vibrations of the arterial wall From the practical point of view if pulses recorded by such a method bear a constant relation to either pressure or volume pulses such a

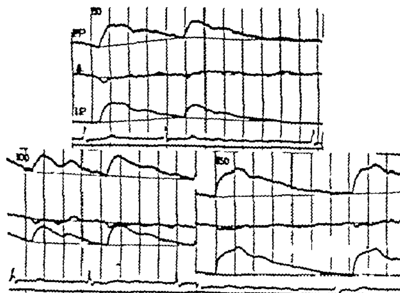


Fig 4 As in Fig 3 from young man with mitral disease trial fibrillation nd ariably slow entricular rate The impedance pulse is recorded between a Cournand needle and small skin electrode over the tip of the needle the subtraction curve is in the center in all three sections Time lines in 0.2 second

technique would have practical advantages over the more cumbersome arterial puncture or subcutaneous impedance plethysmography (for recording pressure and volume pulses, respectively).

The results herein indicate that pressure plethysmograms have contours identical to intra-arterial pressure pulses only at cuff pressures less than 20 mm. Hg; inasmuch as at such low pressures the gain of the amplifiers has to be quite high and base-line stability is poor, this similarity is mainly a matter of theoretical interest. For practical purposes it is important to note that over a wide range of cuff pressures the recorded pulses are changes in volume because (a) their onset precedes that of the pressure pulse, much as arterial impedance (volume) pulses do, and (b) their contour has the same relationship to the arterial pressure pulse contour from the same locus as does a purely volume pulse (see preceding paper[4]).

On the other hand, comparison of pressure plethysmograms with arterial impedance pulses obtained with the technique described in this and the preceding paper indicates that only minor differences exist; these are not accentuated with increase in cuff pressure or during arrhythmias. Such differences are probably related to the dissimilarity of the recording techniques; in fact, the impedance plethysmogram will record any resistivity change between the two electrodes, whereas the pressure plethysmogram will record mainly outward arterial expansion underneath the area of the cuff. It is likely that resistivity changes may occur without gross outward arterial expansion. If these inconstant differences in contour are disregarded, the similarity between pulses obtained with the two methods indicates that each method can substitute for the other and that they both record changes in arterial volume.

It is debatable whether tracings obtained with older methods, such as the "Spiegelsegmentkapsel" of the German authors of the twenties,[4] can be classified into the low cuff pressure or high cuff pressure types of pressure plethysmograms. An equally important factor altering the contour of the recorded pulses is the frequency response of the optical segment, or of the totality of the components of the modern cuff systems, tubing, amplifiers, and end recorders. In a photographic and aneroid system such as the one employed in this study, the only moving mass is the diaphragm of the transducer; as long as the dry mechanical resonance of the transducer is several hundred cycles per second, the response can be said to be flat to at least 20 per cent of the natural frequency.[7] High-frequency oscillations approaching the natural frequency of the gauge and inducing artefacts from resonance are not expected to occur in the system under study, and, indeed, impedance plethysmograms able to record much faster oscillations are devoid of them.

Summary

1. Comparison of contours of the following *height-equalized* pulses from the brachial artery has been made: (1) an intra-arterial pressure pulse versus an external pressure plethysmogram; (2) a pressure plethysmogram versus an impedance plethysmogram. Fifteen healthy young men and 8 men with cardiovascular disease were studied in this manner.

2. *Intra-arterial pressure pulses versus pressure plethysmograms.* At cuff pressures of 20 mm. Hg or less the contours by the two methods were identical in about two thirds of the cases; in the others the pressure plethysmograms were relatively larger throughout most of each cycle, even though their peak height was adjusted to equal that of the intra-arterial pressure pulse. With higher cuff pressures this relation became constant, i.e., all pressure plethysmograms had areas larger than those of the corresponding height-equalized pressure pulses. When pulses with unequal volume output were compared, as in the case of arrhythmias, the ratio of the pulse sizes with the two methods varied considerably. In every case the pressure plethysmogram preceded the corresponding intra-arterial pulse; this interval was variable and depended directly on the level of intra-arterial pressure at the moment of the ectopic beat.

3. *Pressure plethysmograms versus impedance plethysmograms.* Pulses obtained with either one of these methods were quite alike, and there was no trend in the minor differences in contour which were

occasionally observed even when the applied cuff pressure was varied between considerable levels

4 These data indicate that pressure plethysmograms and arterial impedance plethysmograms obtained with the techniques described herein are arterial volume pulses and differ from pressure pulses recorded from within the same vessel They may provide further information on the properties of the artery under study in addition to the information obtained by methods of intra arterial pressure recording

REFERENCES

1 Dontas A S Comparison of simultaneously recorded intra arterial and extra arterial pressure pulses in man Am Heart J 59 576 1960
2 Kettner M G Ferraro C and Dochoval P W Clinical investigation by the oscillogram of peripheral arteries Am Heart J 49 485 1955
3 Dontas A S and Cottas C S Arterial volume and pressure pulse contours in the young human subject Am Heart J 61 6 6 1961
4 Frey W Der arterielle und capillare Puls I Bethe Bergmann Handbuch der normalen und pathologisch n Physiologie Berlin Springer 1223 1927
5 Daoud G Reppert E H J and Scott Butterworth J Basal systolic murmurs and the carotid pulse curve in the diagnosis of calcareous aortic stenosis Ann Int Med 50 3 3 1959
6 Karpman H L Payne J H and Winsor T A practical systematic laboratory approach to the study of the peripheral circulation Ann Int Med 53 306 1960
7 White G Response characteristics of simple instrument Statham Instrument Notes N 2 1948

Contribution of the right ventricular wall to the QRS complex

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The extent to which the right ventricle contributes to the QRS complex is the subject of some disagreement. Some conclusions concerning this contribution have been based on the changes in the early portion of QRS during right bundle branch block. Right ventricular depolarization, which normally occurs early in ventricular activation, is postponed until late in the QRS after experimental right bundle branch block. It follows that if the right ventricle contributes potentials to early QRS, the early as well as the late part of QRS should be altered when this bundle is blocked. Since all parts of QRS are altered after experimental right bundle branch block, it would seem that the right ventricle does contribute measurably to QRS. Clinical right bundle branch block, however, produces no abnormalities in the early QRS. Grant compared electrocardiograms recorded during normal conduction and during right bundle branch block in the same individuals and found no alteration of early QRS. Sodeman and associates[1] found that the first part of the QRS was altered in only 2 of 23 patients with right bundle branch block. To resolve this conflict, Grant postulates two types of clinical right bundle branch block. He feels that the more common type, in which the early part of QRS is unchanged, probably results from a peripheral block, and that the less common form, which is associated with alteration of the initial QRS, is due to block of the right bundle.

Separation of the contribution of the right free wall alone from that of the right free wall *and* septum has rarely been attempted. In the only pertinent animal experiment, Boden and Neukirch[4] found definite changes in Lead II after they removed the free right ventricular wall from the perfused canine heart.

The purpose of the present investigation was to study the electrocardiographic contribution of the free right ventricular wall and that of the right septum. To demonstrate the contribution of the right wall, electrocardiograms were recorded before and after excision of the wall from (a) the perfused dog heart and (b) the dog heart in situ. To show the contribution of the right septum, the right bundle (in the perfused heart) was incised after the removal of the wall.

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Materials and methods

Excision of the right wall in the perfused heart. Ten hearts from mongrel dogs were perfused in a cylindrical plastic bath 12 cm. in diameter and 13 cm. high. A donor dog provided the perfusing blood, which was maintained at 37° 39 C. The perfused heart was suspended from a Palmer vertical micromanipulator which was used to raise and lower the heart. Electrodes were attached to the anterior, posterior, left, right, and bottom (apical terminal) of the plastic cylinder. An electrode attached to the aorta served as the top (basal) terminal. Unipolar leads were recorded between these terminals and a modified Wilson central terminal (indifferent lead). This central terminal was constructed by connecting each of the 6 electrodes through a 10,000 ohm resistor to a single terminal. Bipolar leads were recorded between the anterior and posterior, the left and right, and the bottom and top terminals.

Electrocardiograms were recorded on either a 12 channel Rycom oscilloscope, a 16 channel oscilloscope,[4] or an 8 channel Offner oscillograph. The film and paper speeds were between 50 and 500 mm. per second. Although more detail could be seen at the faster speed, 50 mm. per second was adequate for interpretation of changes in the direction of depolarization. Since the QRS is shorter in the dog than in man, the speed of 50 mm. per second produced QRS complexes roughly as long as those recorded at the conventional speed of 25 mm. per second in human subjects. To check the position of the heart at various times during the experiment, an artificial bipole was created on the surface of the heart by sewing electrodes in its apex and base and connecting them to a sine wave oscillator. The sine wave voltage was recorded from the electrodes attached to the surface of the cylinder. Any change in cardiac position would change these records. After the heart was placed precisely in the center of the perfusion cylinder, control electrocardiograms and control records of the oscillator voltage were obtained.

The heart was then elevated and the free right wall was removed by cutting as close as possible to the septum and atrial border. After the heart was lowered to its preoperative position in the bath, the QRS complexes and the voltages from the oscillator were recorded. Since the tracings of voltages from the oscillator indicated that position of the heart could be precisely controlled with the micromanipulator, the use of the artificial bipole was thought to be unnecessary in the last 6 experiments. During these experiments the heart was positioned by direct measurement. As noted in Fig. 1, short recording time constants were at times used postoperatively in order to minimize the S-T displacement due to injury. This procedure did not alter the QRS complexes.

In order to determine what portion of a record was altered, a time reference voltage was recorded simultaneously with the electrocardiograms from the left ventricular wall. In the study of the records and the preparation of illustrations, the time reference voltages were placed vertically above one another.

In 4 experiments the right bundle was cut after removal of the right wall, and electrocardiograms were then recorded.

Substitution of a prosthesis for right wall in living dog. Acute experiments were performed on 2 mongrel dogs which weighed 10 and 13 kilograms. They were anesthetized with pentobarbital and maintained by artificial respiration. Four electrodes were sewn to the intercostal musculature in order to eliminate movement during the procedure. Unipolar potentials were recorded between the body surface electrodes and a modified Wilson central terminal. An Offner multichannel ink writing oscillograph was used so that complexes could be studied during the procedure.

To determine whether thoracotomy alone might alter the electrocardiogram, preliminary control experiments were performed on both animals as follows. After preoperative control tracings were made, the thorax was opened by a midsternal incision, and the pleural and pericardial cavities were entered. The heart was manipulated and then returned to its previous position. The sternum and the overlying skin were then carefully approximated. A small opening was maintained in the middle of the incision so as to allow the air from the pleural space to escape while the lungs were inflated by clamping the outlet of the respirator. When all air appeared to

been removed from the pleural space the wound was closed completely and a second group of tracings was taken Since the postoperative complexes were similar to those recorded preoperatively the thorax was reopened and replacement of the free right ventricular wall was begun A sheet of chamois the size of the wall was fastened with continuous silk suture to the borders of the free right wall The wall was then removed through a large incision in the chamois while the venae cavae were occluded The prosthesis was quickly closed with silk suture and blood was removed from the pleural space The thorax was again closed and the air it contained was expelled A third group of tracings was then taken

Results

These results will be discussed solely with reference to changes early in QRS No consistent changes in any leads were noted late in QRS in this study

Effects of excision of right wall from perfused heart

RIGHT AND LEFT LEADS Activity during the initial half of QRS was directed more leftward after the right wall had been removed in all 10 experiments A typical result is illustrated in Fig 1 *a* through *f* and in Fig 3 The control tracing from the right lead (Fig 1 *a*) was positive negative during the first half of the QRS complex In the postoperative tracing (Fig 1 *b*) the complex was negative throughout the first half of the QRS interval Reciprocal changes appeared in the left unipolar lead The control left lead (Fig 1*d*) was negative positive during the first half of QRS and the postoperative tracing (Fig 1 *e*) was positive during the entire first half of QRS

APICAL AND BASAL LEADS In 9 of the 10 experiments the activity was directed more basally after removal of the wall Sample records are shown in Fig 1 *g* through *l* In the control tracing from the apical lead (Fig 1 *g*) the entire first half of QRS was positive After the wall was removed the amplitude of this potential was markedly reduced and indeed the lead (Fig 1 *h*) became positive negative during the first half of depolarization Reciprocal changes were seen in the basal lead The potential was negative and then slightly positive during the first half of the QRS in the control tracing (Fig 1 *j*) The postoperative potential (Fig 1 *k*) was positive during this period In the exceptional experiment there was no change of direction along the apico basal axis Inspection of the formalin fixed specimen revealed that less of the wall had been removed from this heart than from the others In a later experiment the wall was removed in two equal sections typical changes in the apical and basal unipolar leads did not appear after removal of half of the wall but did appear when all of the wall was extirpated

ANTERIOR AND POSTERIOR LEADS In 5 experiments the postoperative activity was directed more posteriorly during the first half of QRS and in the other 5 experiments the postoperative activity was directed more anteriorly In the record shown the control tracing from the posterior lead (Fig 1 *m*) contains a small positive deflection and then a larger positive component during the first half of the QRS In the postoperative complex (Fig 1 *n*) the first half of QRS was initially moderately positive then isoelectric and then positive again The control tracing from the anterior lead (Fig 1 *p*) was positive during the first half of ventricular depolarization and in the postoperative tracing (Fig 1 *q*) the first half of QRS was negative Activity therefore was directed more posteriorly after the wall was removed in this heart

Right bundle branch block after excision of right wall from perfused heart Although the QRS was prolonged after right bundle branch block the early portion of QRS could be identified and compared with the early QRS under the preceding conditions The direction of depolarization changed to the right after the bundle was cut This happened in 3 of the 4 experiments In the exceptional heart there was essentially no change In both the right and the left lead the complex after bundle branch block approximated more closely the control than the complex seen after removal of the wall alone The changes shown in Fig 1 are representative of this series of experiments The first half of the QRS from the right lead (Fig 1 *b*) which was negative after excision of the wall became positive (Fig 1 *c*) after the bundle was incised In the left lead the change was from positive

(Fig 1 e) to negative (Fig 1 f) during the entire first half of QRS After right bundle branch block the projection of the potentials in the basal apical direction was smaller (Fig 3) The projections along the left right and anterior posterior axis were also smaller after the block In the apical lead the early half of QRS was slightly more positive (Fig 1) after than before the bundle was cut (Fig 1 k) In the basal lead the QRS complex returned from a positive configuration (Fig 1 k) to negative positive (Fig 1 l) after the bundle was cut The activity was directed more anteriorly after incision of the bundle as indicated in m through r of Fig 1 This was not a constant finding in 2 experiments activity was directed more posteriorly during the first half of QRS The changes during the latter half of depolarization were much smaller than those during the first half

Substitution of a prosthesis for free right wall in situ The complexes recorded after simple thoracotomy and closure differed very little from the preoperative control tracings For the lead *most* changed by the thoracotomy there was a correlation of 92 between the complexes before and after the thoracotomy After removal of the wall early depolarization was directed more toward the left in both animals (Fig 2) Preoperatively the first half of the QRS in the right lead (Fig 2 a) was positive the right lead was negative in early QRS after the chamois was substituted for the free right wall (Fig 2 c) Reciprocal changes occurred in the left lead During early QRS the left lead was more positive after (Fig 2 f) than before (Fig 2 d and e) the wall was removed The vector of depolarization was directed less toward the apex after the operation in both experiments Potentials from the apical lead during the first half of QRS were more positive preoperatively (Fig 2 g) than post operatively (Fig 2 i) The initial part of

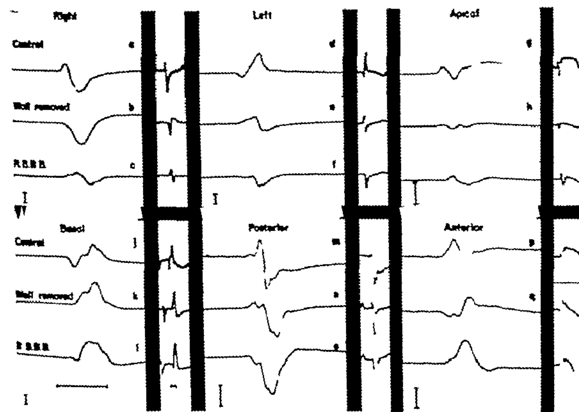


Fig 1 Typical electrocardiogram from the cylinder containing the perfused heart Labels indicate the normal records and those taken after removal of the wall and after removal of the wall and bundle branch block. Horizontal calibrations represent 50 milliseconds and the vertical calibration represents 1 millivolt As indicated records are aligned through the use of a left ventricular time reference potential Discussion in text

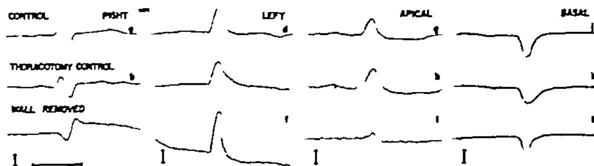


Fig 2 Typical electrocardiogram from the body surface of the [illegible] heart dog. Control before thoracotomy; thoracotomy control taken after thoracotomy had been repaired. [illegible] removed from heart [illegible] removal record was taken after [illegible] had [illegible] for the right wall. Horizontal calibration represents 80 millisecond and vertical calibration represents 1 millivolt. Discussion in text.

QRS of the basal lead was more negative preoperatively (Fig. 2 *j* and *k*) than postoperatively (Fig. 2 *l*). Thus the changes in the QRS recorded at the body surface were very similar to those recorded from the cylinder when the wall was removed from the perfused heart.

Discussion

Plots of normal ventricular depolarization[4] indicate that the free right wall depolarizes from the inside out early in QRS. This inside-out depolarization, which begins in the apical portions of the wall, produces a wave of activity directed toward the right and toward the apex of the ventricle. In these experiments, activity *after the removal of the right wall* was directed more toward the left and basally during the first half of QRS, which is consistent with the picture of early depolarization.

During normal depolarization the right septum depolarizes from right to left and from apex to base.[4] If the right bundle is cut after the wall is removed, this right septal depolarization will be delayed. Therefore, the interruption of the bundle counteracts the effects of removal of the free right wall and tends to return the individual complexes toward normal configuration during the early portion of QRS. The complexes do not, however, return to the exact preoperative configuration. Thus the contributions of the free wall and septum are not exactly equal and opposite. Further more, as can be seen in Fig. 3, the initial *vector* of depolarization is not returned to normal. Similarly, in experimental right bundle branch block, when the early contribution of both the free right wall and the septum is delayed, the configuration of the early portion of the QRS is altered. It should be noted that the left-to-right contribution of the free wall is stronger than the base-to-apex contribution, as demonstrated by one experiment in which the base-to-apex change occurred only with removal of additional tissue.

The uncertainty regarding the normal contribution of the right wall can be attributed in part to the fact that it has not always been considered apart from the contribution of the entire right ventricle. Although there is a substantial amount of activity in the free right wall early in QRS, *the magnitude of the potential produced* by this activity is lessened by oppositely directed depolarization in the septum. Nevertheless, it does appear that functional loss either of the free right wall or of the free right wall and septum should be electrocardiographically detectable, but it is not necessarily true that the presence or absence of activity in either or both of these structures could be detected on the basis

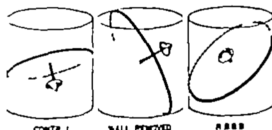


Fig. 3 Vectorial representation of initial direction of ventricular activation in the normal, after removal of the right wall and after right bundle branch block.

of present standards for normalcy if no control tracing were available

Although cutting the right bundle after removal of the free right wall does not duplicate right bundle branch block or any other known clinical lesion this maneuver provides some information concerning right septal depolarization in the dog When the bundle is cut after the wall is removed the QRS complex is prolonged by about 12 milliseconds between 25 and 33 per cent of the normal duration It is thus clear that the right septum makes a sizable contribution to the QRS complex This observation provides further evidence against the claim[8] that the septum depolarizes almost entirely from left to right This finding does not limit the duration of right to-left septal depolarization to 12 milliseconds but this does appear to be a minimal duration of this phase of septal activity

The study reported on in this paper can be considered an extension of the investigations of Jacobson and his co workers[7] who used plots of the normal ventricular depolarization to predict the electrocardiographic effects of lesions at various sites in the left ventricle They then attempted to correlate these predictions with post mortem studies on individuals who had had myocardial infarcts Jacobson and his co workers considered the correlation adequate or good Although the lesion which we produced does not occur clinically the amount of the tissue removed was definitely known so that changes were easily correlated with the plot of ventricular depolarization Like the previous investigators we believe that we found a good agreement between the actual and predicted effects of the lesions

A significant finding during these studies was that thoracotomy alone does not alter the electrocardiogram if air is completely removed from the thorax Similarly Wilson and Meek found that thoracotomy in acute canine experiments does not alter the bipolar limb leads It follows that certain types of experiments which might superficially seem to require chronic experimentation can be acutely performed

Our experiments leave unanswered two important questions (1) Why is the early portion of QRS usually unchanged in the clinical syndrome characterized by marked prolongation of QRS with forces directed to the right late in the complex (2) What types of lesions account for the clinical syndromes in which depolarization is somewhat prolonged but not so greatly prolonged as in experiments in which the right bundle is cut?

Conclusions

The direction of depolarization in the first half of QRS is directed more to the left and basally after removal of the free right ventricular wall in the perfused dog heart and in the intact dog The right septum contributes significantly to the QRS since cutting the right bundle after the wall was removed changed the first part of QRS

The authors are indebted to Mr Otis F Brown for his valuable technical assistance

REFERENCES

1. Barker J M and Valencia F The precordial electrocardiogram in incomplete right bundle branch block Am Heart J 38 376 1949
2. Grant R P Clinical Electrocardiography New York 1957 McGraw Hill Book Company Inc pp 119 123
3. Soderman W A Johnston F D and Wilson F N The Q1 deflection of the electrocardiogram in bundle branch block and axis deviation Am Heart J 28 71 1944
4. Boden E and Neukirch P Elektrokardiographische Studien am isolierten Saugetier und Menschenherzen bei direkter und indirekter Ableitung Pflüger Arch ges Physiol 171 146 1918
5. Scher A M and Young A C Ventricular depolarization and the genesis of QRS Ann New York Acad Sc 65 68 195
6. Erickson P V Scher A M and Becker R A Ventricular excitation in experimental bundle branch block Circulation Res 5 5 1957
7. Jacobson E D Rush S Zinberg S and Abildskov J A The effect of infarction on magnitude and orientation of electrical events in the heart Am Heart J 58 863 1959
8. Meek W J and Wilson A The effect of changes in position of the heart on the QRS complex of the electrocardiogram Arch Int Med 36 614 1925
9. Medrano G A Bisteni A Brancato R W Pileggi F and Sodi Pallares D The activation of the interventricular septum in the dog heart under normal conditions and in bundle branch block Ann New York Acad Sc 65 804 1957

U vector loop or arc in normal subjects and in those with left ventricular hypertrophy

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Although most of the electrocardiographic deflections have been studied by vectorcardiography, we are not aware of any systematic study on the U vector loop or arc. This is because the U loop is very small and merges with the ST, T, and P loops and the initial and terminal portions of the QRS loop. The method of differential vectorcardiography[1] has enabled us to study the morphology of the U loop. In this research the characteristic features of the U loop of the normal heart and of left ventricular hypertrophy were studied.

Materials and methods

U loop vectorcardiograms were obtained from 61 subjects. These subjects showed a pulse rate of around 60 to 80 per minute. Those with a faster pulse rate were excluded because of the difficulty of dissecting the U loop. All subjects had a sinus rhythm. Of these, 30 were normal healthy subjects and the other 31 had left ventricular hypertrophy. Their ages and sex distribution are shown in Table I. Most of the former group were medical students and house officers. In the latter group the diagnosis of left

Table I. Age and sex distribution of all of our subjects

Diagnosis	*Sex*	*Age (years)*							*Total number of subjects*
		11-20	*21-30*	*31-40*	*41-50*	*51-60*	*61-70*	*71-80*	
Normal	Male	2	21	3	1	—	—	—	27
	Female	—	1	1	—	—	1	—	3
Left ventricular hypertrophy	Male	—	2	—	5	10	6	1	24
	Female	—	—	—	2	4	1	—	7

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ventricular hypertrophy and mostly dilatation was made on the basis of chest roentgenograms conventional 12 lead electrocardiograms and the results of physical examination including determination of blood pressure in each subject This group was composed of 23 cases of essential hypertension 2 cases of renal hypertension 1 case of mitral insufficiency and 1 case of combined valvular disease The other 4 subjects showed a complication of myocardial infarction and were excluded from this study which sought for the vectorcardiographic features due to ventricular overloading itself

Left ventricular hypertrophy was classified tentatively into three grades according to its severity Grade I included the cases in which slight left ventricular enlargement was noted on the chest roentgenograms and by physical examination The electrocardiograms either could not be said to show left ventricular hypertrophy or could be said to do so only after various measurements had been taken and checked with the criteria of left ventricular hypertrophy proposed by Sokolow and Lyon The cases in which only the roentgenogram or electrocardiogram revealed slight or moderate left ventricular hypertrophy were also included in this grade Grade II included the cases in which moderate left ventricular enlargement was observed on the chest roentgenograms and by physical examination The electrocardiograms in these cases showed sufficient evidence of left ventricular hypertrophy but the findings indicated a moderate hypertrophy not presenting the typical S T segmental depression and T wave inversion The cases in which two of the three items i e the roentgenogram electrocardiogram and results of physical examination revealed moderate or fairly marked left ventricular hypertrophy were included in this grade Grade III included the cases which showed marked left ventricular enlargement on the chest roentgenograms and by physical examination The electrocardiograms in these cases revealed also marked left ventricular hypertrophy showing S T segmental depression and T wave inversion The cases in which all of the three items revealed moderate left ventricular hypertrophy were also included in this grade

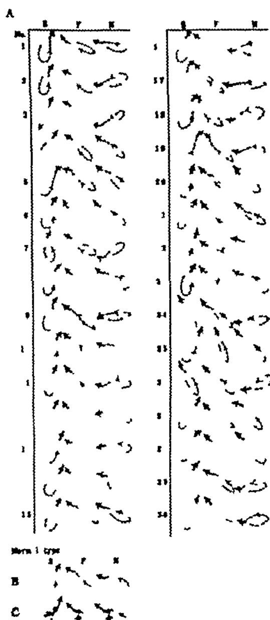


Fig 1 Diagrams of the T U vector loops in all of our normal cases Short solid lines with arrow on their tips show the U vector loops and broken lines the T vector loops Arrows indicate direction of inscription Numbers show those of normal case S Sagittal plane F Frontal plane H Horizontal plane Almost all cases can be regarded as having configuration such as that shown in B which has can be called the normal type There were 7 exceptional cases Case 24 through Case 30 which showed counterclockwise inscription of the T loop in the frontal plane. However even in these cases the U loop does not look different from that of other normal cases As for C see text.

Table II. T-U vector loop of left ventricular hypertrophy. Summary of features in all three planes and relationship to the severity of left ventricular hypertrophy

Grade of left ventricular hypertrophy	Normal in all planes	Abnormal T-U loop: T-U loop concordant with QRS including cases of abnormality of U loop only — Abnormal in two or three planes	Abnormal T-U loop: T-U loop concordant with QRS including cases of abnormality of U loop only — Abnormal in one plane	Abnormal T-U loop: T loop discordant with QRS — Abnormal in any one of planes
I	0	0	1	0
II	1	9	4	3
III	0	1	1	6
Total number of cases	1	10	6	9

Vectorcardiograms were taken in all cases by the method proposed by Frank.[8] After the whole vector loop amplified at a magnification of 1 mv. to 0.7 inches was photographed in each case, the monitor electrocardiograms of our dissecting apparatus were dissected from the beginning of the T wave to the end of the U wave and the corresponding part of the vector loop was amplified to the higher magnification of 1 mv. to 2.8 inches and photographed. This part of the vector loop will be called the *T-U vector loop* in this paper. Next, only the U wave was dissected and its loop was also photographed at this higher magnification. Three planar projections were always photographed at the same time. Simply taking pictures was not sufficient to reveal the direction of inscription of the U loop, and careful observation of the dissected U loop or T-U loop on the cathode ray oscilloscope was usually necessary. The time constant of our vectorcardiograph was arranged so as to be as long as 2.8 seconds in order to avoid distortion of such minute loops.

Results

By means of dissection the U loop could be noticed after accumulated experience in all except one case in which no definite direction of the beam spot movement could be noticed because it was too minute.

After the T loop was inscribed, the beam spot appeared to stay for a moment at the T-U junction, which corresponds to the T-U segment of the electrocardiogram; then the U loop was inscribed much more slowly than the T loop. Thus, the T-U junction was always clearly identified.

The U loop of normal subjects resembled a small, slightly curved club and was inscribed almost in the direction of continuation of the terminal limb of the T loop. Slight bending occurred, especially in the sagittal plane, at the T-U junction, differentiating the U loop from the T loop.

According to the configuration just described, a term such as *U vector segment* or *U vector arc* might be preferable to the term *U vector loop*. However, since none of the other components of the vectorcardiogram have been so called, even though, for instance, some abnormal ST-T loops are actually arc shaped, the term *loop* was used in this paper.

The T loop of normal subjects was directed to the left, inferiorly, and anteriorly or slightly posteriorly in its long axis. It was inscribed clockwise in the frontal plane and counterclockwise in the horizontal and left sagittal planes.

From a glance through the tracings of Fig. 1*A*, all from the normal subjects of this study, it can be realized that the inscription of the U loop in continuation of the terminal limb of the T loop, together with the above-mentioned direction of inscription of the T loop, forms the characteristic feature of the normal T-U loop, which can be shown by the diagram in *B* of Fig. 1. (The vector loop from the beginning of the T loop to the end of the U loop is designated as the *T-U loop* in this

paper.) An example of this feature in a loop from a normal subject is seen in Fig. 2. Loops from all of our normal subjects showed this feature except in 7 cases in which there was counterclockwise inscription of the T loop in the frontal plane. Even in these subjects the U loop was inscribed in continuation of the terminal limb of the T loop as in other normal subjects (Fig. 1 A).

When the end of the U loop is considered as the null point of the whole vector loop, the T-U junction vector, namely, the vector from the null point to the junction between the T loop and the U loop, was directed to the left, inferiorly, and mostly anteriorly. The distribution of this vector in normal subjects is shown in Fig. 3 A, in which the end points of these vectors were plotted, taking their magnitude into consideration.

It is shown that the vectors are distributed mostly in a certain limited extent, ranging from 0 to +90 degrees in the frontal and horizontal planes and from +90 to ±180 degrees in the left sagittal plane. In A and B of Fig. 3, only those cases in which the vectorcardiograms were well photographed were chosen for measurement, but the discarded cases showed a similar tendency.

Which point of the U vector loop corresponded to the peak of the U wave of the electrocardiogram offered a difficult problem. It could never be clearly identified. However, when the dissection was made from some points of the T wave to the peak of the U wave in the monitor electrocardiogram, the vector loop ended not far beyond the T-U junction, but rather close to it. Graphical derivation of the T-U loop from component electrocardiograms showed a slight return movement at the beginning of the U loop in many cases, as is shown in Fig. 1 C, where the tip of the return movement, indicated by white arrows, corresponds to the peak of the U wave. However, in none of our cases was such a return movement definitely visible on the actual cathode ray oscilloscope or in the photographs. It was presumed that the apparent stay of the beam spot at the T-U junction for a moment might be due to this return movement in some cases, which could be clarified at a magnification higher than ours. The fact that the T-U junction was

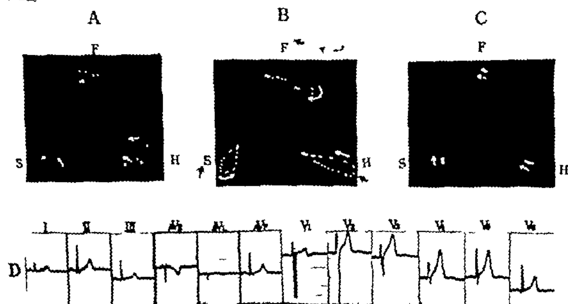


Fig. 2. An example of the T-U loop of a normal 29 year old man. Arrows show the direction of inscription of the vector loop. A, The entire loop. B, The T-U vector loop dissected. In the diagram, short solid lines with arrows on one end show the U loop and the broken lines show the T loop. C, Only the U vector loop was dissected. D, Conventional electrocardiograms taken at standard sensitivity. F, S, and H denote frontal, sagittal, and horizontal planes.

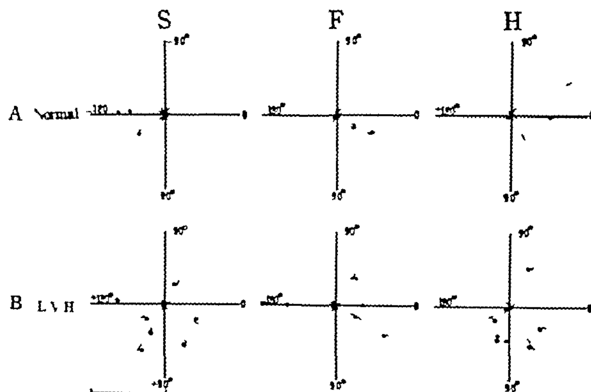


Fig. 3. Distribution of the T-U junction vectors of normal cases (A) and cases of left ventricular hypertrophy (B). When the T vector is discordant with the QRS vector, the T-U junction vector may have a significance different from that when the T vector is normal or concordant with the QRS vector, even if by chance both have the same direction. Therefore, the T-U junction vectors with the discordant T vector are indicated by open circles while others are indicated by closed circles. (For the purposes of this study, when the difference between the long axis of the T and QRS loops in a plane was more than or equal to 120 degrees, the T loop or vector was arbitrarily said to be discordant with the QRS loop or vector, and concordant when the difference was less.) A transverse bar at the left lower corner of the figure indicates the magnitude of 0.1 mv. *S*, *F*, and *H* denote sagittal, frontal, and horizontal planes.

so clearly identified may be due to this tendency. Anyway, since the point of the U loop corresponding to the peak of the U wave was close to the T-U junction and since the recognized U loop was like a small slightly curved club, the direction of the U vector, i.e., the vector from the null point to the point corresponding to the peak of the U wave, was presumed to be almost the same as the T-U junction vector.

In cases of left ventricular hypertrophy, on the contrary, the U loop began with a marked bend at the T-U junction and extended in various directions, resembling also a small curved club but sometimes much larger than normal U loops. In Fig. 4 all the cases of left ventricular hypertrophy are classified according to the manner in which the U loop joined together with the features of the T loop in each plane, and two actual examples are shown in Figs. 5 and 6. Sometimes the U loop was inscribed as in normal cases in the continuation of the terminal limb of the T loop, but in such cases of left ventricular hypertrophy the T loop itself was abnormal, either in the direction of inscription of the loop or in the direction of its long axis, whether it was concordant or discordant with the QRS loop. Because of such bending at the T-U junction or of the abnormal direction of the long axis of the T loop, the direction of the T-U junction vector and the U vector was in many cases different from that in normal cases and was distributed widely, as is shown in Fig. 3,*B*. Thus, if the whole T-U loop is considered, few cases retained normal features, as shown in Fig. 1,*B*. Actually, we could find only one case which retained normal features in all three of the planar projections among the 27 cases of left ventricular hypertrophy, as is seen in

Table II In a few other cases normal features were retained in one projection whereas abnormal features were observed in other projections

Furthermore the following tendency can be observed from Fig 4 and Table II in the group of cases which retained normal features in any one of the planes or which showed abnormality in the U loop only or which showed abnormality somewhere in the T U loop but had the T loop concordant with the QRS loop there were more cases of relatively slight or moderate left ventricular hypertrophy whereas in the group in which the T loop was discordant with the QRS loop there were more cases of relatively marked left ventricular hypertrophy (Fig 6)

In our cases of left ventricular hypertrophy 5 showed a negative U wave and 7 showed a negative T U segment in the electrocardiograms In all of these the U loop began with a marked bend at the junction and was abnormally directed It was noteworthy however that cases in which the electrocardiograms did not show any U wave abnormalities revealed such U loop abnormalities just as markedly (Fig 5)

Discussion

Since almost all of the subjects with left ventricular hypertrophy showed more or less of an abnormality of their T U loop this finding was quite useful for diagnostic purposes *In our cases there were many* subjects who showed no (or minute) evidence of left ventricular hypertrophy in electrocardiographic deflections in spite of definite evidence of left ventricular enlargement in the chest roentgenograms A study of the T U loop in such cases revealed almost all of them to have some abnormality Therefore in the later stage of this study we could predict whether the subject was normal or not by examining the U loop first To some extent we could also predict the presence of left ventricular hypertrophy However we cannot say whether or not such abnormality of the U loop is due to left ventricular hypertrophy Some abnormalities of the U loop indicated old myocardial infarction or other cardiac diseases rather than left ventricular hypertrophy Although the afore mentioned abnormalities seemed to differ from the latter we are not able to correlate specific configuration of the U loop with the various disease states as yet because of our limited experience

That the actual U vector loop does not usually constitute a closed loop differs from our primary expectation as well as that of Furbetta and his associates The reason for this is not completely clear However when the component electrocardiograms were examined at the high magnification of 1 mv to 2 8 inches on the cathode ray oscilloscope the T U segment was frequently not coincident with the base line Even when it was on the base line in

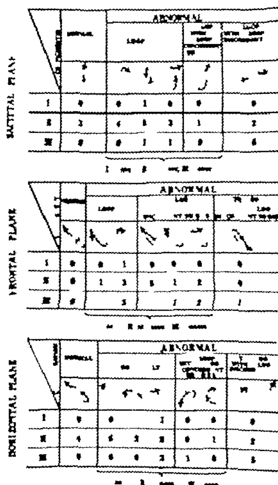


Fig 4 Diagrams of the T U vector loops of left ventricular hypertrophy They were classified on the basis of configuration Number of cases of each grade of left ventricular hypertrophy which showed such configuration is listed in this table In the diagram of the vector loop T loops are shown by broken lines and U loops are shown by short solid lines with arrows on one end

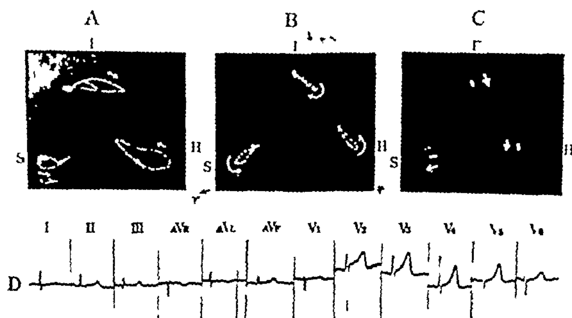


Fig 5. An example of the T-U loop of left ventricular hypertrophy. A case of renal hypertension in a 54 year-old woman. Figure arrangement and abbreviation are the same as in Fig. Major abnormality lies in the direction of the U loop. In this case the electrocardiogram was almost within normal limit including the U wave finding as shown in *D* in spite of the fact that the roentgenogram and physical examination showed marked left ventricular enlargement with systolic pressure of 1 8 and diastolic pressure of 95 mm Hg. However the U vector loop is definitely abnormal.

one component, it was usually not so in the other component perpendicular to this. When an electrocardiograph with a shorter time constant is employed, the end of an actual upright T wave may be recorded more depressed, which may make an actually elevated T-U segment consistent with the base line.

Negative U waves of the electrocardiogram have been regarded by some authors as a more advanced sign than other electrocardiographic abnormalities. For example, Kemp and his associates[4] noticed that negative U waves were found in cases of more severe hypertensive heart diseases and stated that in the evolution of the left ventricular strain pattern the inversion of the U wave is a late event that follows the inversion of the T wave by a certain time lag. They also observed that in the few cases in which an inverted U wave followed a positive T wave, morbidity and mortality were very high. Our clinical experiences were consistent with theirs to some extent. However, our present study suggested that the abnormality of the U vector loop developed long before the appearance of various other electrocardiographic abnormalities including not only those of the U wave but also those of the T wave. Actually, abnormalities of the U loop alone appeared in cases of left ventricular hypertrophy of rather slight degree. Negative U waves in the electrocardiograms can be regarded as a terminal event in the evolution of the changes in the U vector loop. Therefore, it is natural that they have grave prognostic significance. On the other hand, abnormalities of the U loop alone can thus be employed to discover earlier stages of left ventricular hypertrophy.

Summary

1. U loop vectorcardiograms were obtained from 30 normal subjects and from 31 subjects with left ventricular hypertrophy by the method of differential vectorcardiography. Four of the subjects with left ventricular hypertrophy were excluded from the present study because of the complication of myocardial infarction.

2. The U loop of normal subjects showed a constant configuration. It re-

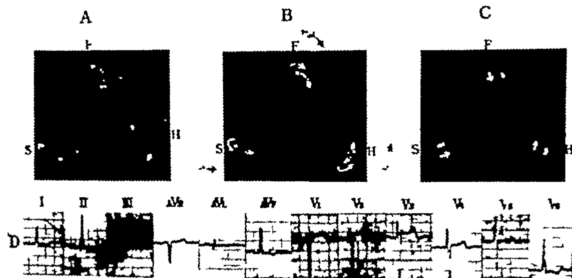


Fig 4 Another example of the T U loop of left ventricular hypertrophy A case of essential hypertension in 67 year-old man Figure arrangements and abbreviations are the same as in Fig 2 The T loop discordant with the QRS loop and the U loop is also abnormal in its direction The electrocardiogram showed marked left ventricular hypertrophy with negative U waves in Lead V and negative T U segments in Lead V V and V The roentgenogram and physical examination also revealed marked left ventricular enlargement

sembled a small slightly curved club and was inscribed almost in the direction of continuation of the terminal limb of the T loop so that a term such as *U vector segment* or *U vector arc* might be preferable to the term *U vector loop* The T U junction vector was directed to the left inferiorly and mostly anteriorly This finding of the U loop together with that of the T loop which was inscribed clockwise in the frontal plane and counterclockwise in the horizontal and left sagittal planes with its long axis directed to the left inferiorly and slightly posteriorly or anteriorly constituted characteristic features of the normal T U loop

3 The U loop of left ventricular hypertrophy began with a marked bend at the T U junction and extended in various directions resembling also a small curved club but sometimes much larger than normal U loops Occasionally the U loop was inscribed as in normal cases in continuation of the terminal limb of the T loop but in such cases the T loop itself was abnormal All cases of left ventricular hypertrophy showed such a feature of the T U loop in at least one planar projection there was one exception however a case in which normal features were retained in all three planes

4 There was a tendency toward relatively slight left ventricular hypertrophy in those cases which retained normal features in any one of the planes or those which showed abnormality in the U loop only whereas there was relatively marked left ventricular hypertrophy in those cases which showed a distinct abnormality also in the T loop

5 Such U loop abnormalities were already evident in the early stage of left ventricular hypertrophy when there were no (or minute) evidences of it in ordinary electrocardiograms including the U wave changes Thus they are useful for diagnostic purposes in detecting slight left ventricular hypertrophy

The authors wish to express their appreciation to Mr Hisashi Ohshima for technical assistance

REFERENCES

1 Hellerstein H K Shaw D and Sano T Direction of ectocardiogram differential ec torcardiography Am Heart J 47 887 1954
2 Sokolow M and Lyon T P Ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads Am Heart J 37 161 1949

3 Frank E Accur t linically practical system for pat il ectorc rdiography Circulation 13 37 1956
4 Furbetta D B falari A Sa tucci F and Solin I Abnormalit of the U w v nd of the T I egment of the electrocardiogr m The syndrome of the papillary muscle Circulation 14 1129 1956
5 Kemp K L Sacrwicz B Bettinger J C Gottlieb H and Bellet S Prognostic sig ificance of negati e U waves the ECG in hypertension Circulation 1 98 1957

Case reports

Functionally corrected transposition of the great vessels without significant associated defects

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Within recent years corrected transposition of the great vessels has been reported with ever increasing frequency. Since Von Rokitansky first discussed the anomaly in 1875, it has been reported and reviewed many times in the world literature. Harris and Farber reviewed [illegible] cases in 1939 and presented a detailed discussion of some of the leading embryologic theories. Subsequent reviews by Cardell, by Anderson and associates, and most recently by Walters and associates[4] have begun to delve into the clinical and physiologic findings associated with this cardiac anomaly.

Corrected transposition is generally considered to exist when, in addition to the reversed anterior-posterior relationship of the aorta and pulmonary artery found in uncorrected transposition, there is associated mirror-image reversal. This mirror-image reversal can occur along the cardiac axis either at the level of the atrium, ventricle, or bulbus and is spoken of as inversion. The distinction between inversion and transposition is made on an embryologic as well as a descriptive basis. To qualify as corrected transposition this inversion must permit venous blood to enter the transposed pulmonary artery and then the lungs. The freshly oxygenated blood must then travel through its respective side of the inverted portion of the heart to the transposed aorta and thence to the systemic circuit. On the basis of this concept several articles have described the four possible types of inversion of the cardiac axis which converts transposition of the great vessels into corrected transposition of the great vessels. These are (1) bulbus inversion, (2) arterial and ventricular inversion, (3) bulboventricular inversion, and (4) arterial inversion. Walters[4] reported that 33 of 44 cases of corrected transposition for which anatomic types were recorded were of the bulboventricular type. Other authors[3] have concurred that this is probably the most common variety.

Fig. 1 illustrates the normal heart in comparison with transposition with bulboventricular inversion. As indicated in the bulboventricular type, the posteriorly placed pulmonary artery arises from a right-sided ventricle with the morphologic features of a normal left ventricle. The

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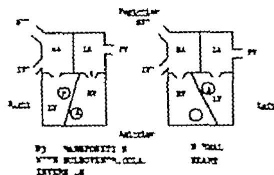


Fig. 1 Diagrammat ill t t f he rela bn of he arion heart hamber nd pre t essed the normal heart and erse ed tran pos tion th bulbo en ricular in ers on

atrioventricular valve on this side resembles a normal mitral valve The anomalously placed aorta in turn arises from the reversed type of situation

Malers further classification of functionally totally corrected transposition is useful and includes only those cases with out associated hunt This means that the aorta now receives only fully oxygenated blood In corrected transposition accompanied by a hunt unsaturated blood may be delivered into the aorta so that the transposition is not totally functionally corrected

We present a case of functionally totally corrected transposition of the great vessel without any ignificant associated defect These crit ria have been met by only 6 of the 4 cases revi wed by Malers and associates and the diagnosis was elucidated by autopsy in each in tance Review of the literature failed to disclose a single case which had been correctly diagnosed clinically Our patient has been closely followed up by his referring physician and has been clinically diagnosed at our Center We present this report in the hopes that our finding some of a different nature than previously reported may hed additional light on the clinical and diagnostic features of corrected transposition by itself Accordingly it is our hope that these findings will aid others in uncovering an interesting cardiac abnormality which may be more common than was heretofore suspected

Case report

Th 11 ear-old boy as first seen t the San Diego Count Heart Center December 1959 for diagnostic tudies H born of normal pregnancy and labor and growth and development ha alw been normal Unconfirmed report ated murmur hich wa heard hen he was 8 month old H remained symptomatic and as first seen by hi referring cardiologist in March 19 3 At that time the findings ere an accentuated second sound t he pulmonic area with Grade (on the ba of 1-6) systolic murmur best heard in the third intercostal pace along with a soft diastolic blowing murmur in the same area X ray films and fluoroscopic tudies t this time revealed globular heart hadow marked fullness in the area of the pulmonary artery and an unu ual prominence of the left superior cardiac border

The patient continued to remain mptomatic he did ell in school and a able t participat in moderately activ port I October 1959 it as thought hat the second sound in the second left intercostal pace had become markedly accentuated The latter was clinicall interpreted as evidence to indicate increa ing pulmonary hypertension, and catheterization arranged Review of the cardiorespiratory system gav entirel negativ finding

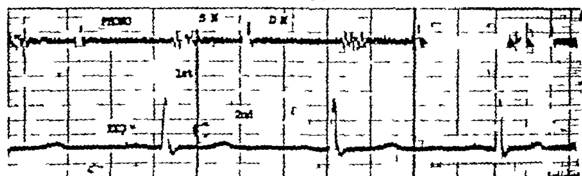


Fig Phonocardiogram showing hort systol murmur accentuated second sound nd decrescendo diastolic murmur

Past medical history and family history were non contributory.

Physical examination revealed a ... lert 11 year old boy in no distress and without gross abnormalities. Cyanosis was not evident. The blood pressure was recorded in both upper extremities at 110/ ... mm. Hg with similar values in the right leg. The pulse was 84 and respirations were 16. The patient was in the sixtieth percentile for height and the fortieth percentile for weight. Examination of the head and neck revealed no abnormal arterial or venous pulsation. The hepatojugular reflex ... negative ... findings were confined to the cardiopulmonary system where minimal left precordial asymmetry was noted. The chest was clear to percussion and auscultation. The point of maximal impulse was located in the fifth intercostal space outside the midclavicular line ... was forceful ... ature and suggest... left ... tricular enlargement. In addition there ... definite lift ... the lower portion of the sternum such as one associates with right ventricular hypertrophy. A striking lift and ... tap were ... noted in the second left intercostal space. Heart tones were audible at all valvular areas and the second sound was markedly accentuated in the second left intercostal space without detectable splitting. A Grade 2 ... stolic murmur was heard maximally in the second left intercostal space and was transmitted ... the ... through to the back. Most notable in the second left intercostal space was ... Grade 4 decrescendo diastolic blowing murmur immediately following the markedly accentuated second sound. The murmur was transmitted down along the left sternal border and could

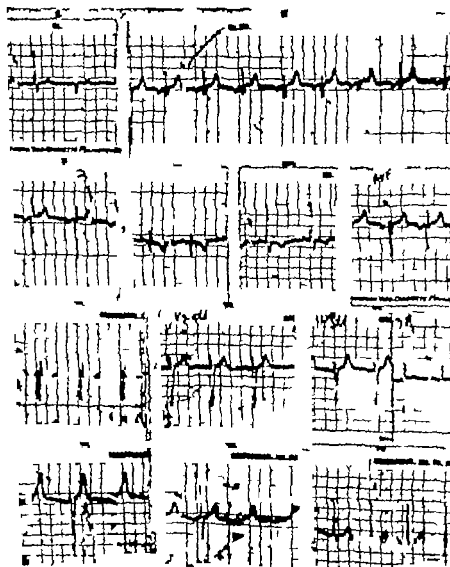


Fig. 3. Routine 13 lead electrocardiogram with portions half standardized. Note tall R waves in Leads I and V... th abnormal R/T ratio in Lead V... suggesting left ven tricular hypertrophy.



Fig 4 Posterior anterior view of chest with barium swallow. See text for description



Fig 6 Posterior anterior projection. Spot film of catheter entering from left ... and terminating ... right pulmonary artery

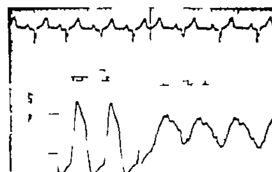


Fig 5 Pressure tracing from right ventricle and pulmonary artery ... insufficiency suggested



Fig 7 Lateral projection of catheter ... Fig 6

be heard at the tricuspid area as well as at the left infraclavicular area. The peripheral pulses were regular and of normal quality without peripheral signs to suggest aortic insufficiency. The remainder of the physical examination as well as laboratory studies gave unremarkable findings.

A phonocardiogram (Fig 2) substantiates the auscultatory findings. The electrocardiogram (Fig 3) demonstrated a normal rate and rhythm. The P-R and QRS intervals were within normal limits. The findings showed definite left ventricular hypertrophy with associated ... pattern as noted in Lead V... The R R complexes ... Lead V... and V... were attributed to rotational changes and this was ... reflected in Lead V... and V... as shown by the slurred S_1 with transition zone shifted to the left. A normal progression of the R ... as present across the precordial leads. The P ... version in Lead II, III and V... was thought to represent normal ... however the possibility of an ectopic supraventricular pacemaker could not be ruled out.

Fluoroscopy demonstrated a globular heart with prominent elongated and convex left superior

Table I. Cardiac catheterization data

Location	Pressure (mm Hg) systolic/diastolic—mean	Oxygen (vol %) (1 in Slyke)	Oximetry (double scale)
SVC	——	11 37	72 4
IVC	——	11 95	78 0
Right atrium	3/3 —5	11 22	71 0
Right ventricle	23/5 —11	11 61	72 3
MPA	19/12—5	11 67	72 3
Brachial artery	127/69—88	15 61 (94 2 sat)	95 0

C di ml 4 86 L/m /M
Pulmonary ml 4 86 L/min M
T tal pulmo ary tance 3 3 dyn ec cm
T tal periphe al st nce 1,309 dynes cm

cardiac border Forceful pulsations wer seen most strikingly in the rea normall occupied by the main pulmonary artery however this represented vig orous aortic pulsations A posterior anterior iew of the chest (Fig 4) showed normal transverse cardiac diameter and the med ll placed pulmonary artery caused a characteristic notch on the barium filled esophagus The proximal indentation that caused by the transverse portion of the aort Ap propriate lateral iew of the chest demonstrated unusual encroachment on the retro ternal pace as well as some posterior d placement by the entric ular mass Selectiv right or left entricular enlarge ment could not be distinguished from the con en tional films

Catheterization and angiocardiography Ca diac catheterization (see Table I) th angiocardiography as performed on Dec 22 1959 Pressures and samples from the entire right side of the heart and peripheral arteries were normal Neither m m pulmonary arterial right entrical brachial arterial pres ur curves suggested insuffic ency of either the pulmon or aortic al es (Fig 5) N in tracardiac shunts were demon trated The abn rmal path of the catheter as the only remarkable find ng A posteroanterior iew (Fig 6) showed the catheter entering an pparently normall placed right trium making harp bend over the spine and exiting int the pulmonary artery through the mediall placed location of the latter essel The lateral iew (Fig 7) showed the catheter ag in the normal egi of right atrium entering the right entricle but then making sharp-bend out f m p steriorly pl ed pulm ary artery F tal nd l teral giocardio grams ere obtained La al iew (Fig 8A) showed the opacit t of the right ided trium and entricle in norm l sequence The right-sided entricle showed m oothness of the ll th lack of ell-defined l ndibulum and with tail-like pes The pulmonary artery given off post riorl Opa t i f the left sided trium and entricle (Fig 8B) in normal sequence with the endocardial surface ppea ng more trabecu l ted tha the right sided entri le Ther as



Fig 8A Lateral angiocardiogram with injection ia cardiac catheter Right-sided event See text for discussion



Fig 8B Lateral angiocardiogram making left heart and aorta



Fig. 9A. Frontal angiocardiogram showing right heart and lesser circulation. See text for full description.



Fig. 9B. Frontal angiocardiogram ... left heart and aorta.

well-defined infundibulum at the outlet of the anteriorly placed aorta. Frontal view (Fig. 9A) demonstrated a medially placed pulmonary artery. A lateral view (Fig. 9B) showed the aorta arising from a left-sided ventricle in which a sharply demarcated infundibulum could be identified as well as the above mentioned increased trabeculations. The angiocardiograms were thought to demonstrate corrected transposition of the great vessels with ventricular and bulbus inversion.

Discussion

The asymptomatic course of this 11-year-old boy demonstrates a possible reason for the paucity of reports of functionally totally corrected transposition without significant associated defects. The 6 cases reviewed by Maleri[4] were diagnosed at autopsy; the ages of the patients ranged from 26 to 60 years, with indications that at least 2 out of the 6 died of noncardiac causes.

We have attributed the diastolic murmur to probable pulmonic insufficiency while keeping in mind the failure to demonstrate this at catheterization. The long-term clinical consequences of pulmonic insufficiency, as noted in a recent article by Collins and associates, are not usually considered to be serious.

An electrocardiographic finding worthy of comment in our patient is the absence of atrioventricular block. Varying degrees of atrioventricular block was often noted as an important electrocardiographic diagnostic feature in most previous case reports describing corrected transposition.[4-17] The left ventricular strain pattern also merits comment in view of the speculation that this may well be associated with the fact that an anatomic right ventricle is handling the systemic load. It is also worthy of note that except for the physical signs of increasing pulmonary hypertension, which are probably due to the unique anatomic arrangement, this patient's condition might not have been diagnosed at this time. Suffice it to say that angiocardiography accompanied by the anomalous route of the catheter on the right side of the heart are the final means of diagnosis.

We conclude this report with the observation that the heart is normally a well designed and durable pump. It has in the case of this boy, by a unique variation which Nature seldom allows, recreated its arrangement to perform its total function adequately merely by substitution and rearrangement of parts. An anatomic right ventricle pumping at a systemic pressure leaves to pure speculation how long this patient's variation can continue to duplicate nature's normal arrangement.

Summary

The various clinical, electrocardiographic, radiologic, angiocardiographic, and cardiac catheterization features in a case of functionally totally corrected transposition

without any associated defects are presented. To our knowledge this is the first case in which detailed studies are available and in which a diagnosis has been feasible ante mortem.

The authors wish to thank Dr. William C. Cooke for the privilege of studying his patient and Mr. Harold W. Hartman for his aid in preparing the manuscript.

REFERENCES

1. Von Rokitansky, C. F.: Die Defekte der Scheidewände des Herzens. Vienna, 1875, W. Braumuller.
2. Harris, J. S., and Farber, S.: Transposition of the great cardiac vessels with special reference to the phylogenetic theory of Spitzer. Arch. Path. 28:427, 1939.
3. Cardell, B. S.: Corrected transposition of the great vessels. Brit. Heart J. 18:186, 1956.
4. Anderson, R., Lillehei, C. W., and Lester, R. G.: Corrected transposition of the great vessels of the heart. A review of 17 cases. Pediatrics 20:626, 1957.
5. Makers, E., Björk, V. O., Callned, I., and Lodin, H.: Transposition functionally totally corrected associated with mitral insufficiency. Am. Heart J. 59:816, 1960.
6. Kahn, M., Henry, E., Grasenas, N. V., and Steinfeld, L.: Atresia of the left atrioventricular valve associated with corrected transposition of the great vessels. Am. J. Med. 28:1013, 1960.
7. Kjellberg, S., Mannheimer, E., Rudhe, U., and Jonsson, B.: Diagnosis of congenital heart disease. Chicago, 1959, Year Book Publishers, Inc.
8. Schaeffer, J. A., and Rudolph, L. A.: Corrected transposition of great vessels. Am. Heart J. 54:610, 1957.
9. Collins, N. I., Braunwald, E., and Morrow, A.: Isolated congenital pulmonic valvular regurgitation. Am. J. Med. 28:159, 1960.

Large abscess of the heart and spleen complicating bacterial (enterococcal) endocarditis

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Myocardi l abscesses re distinctly un common nd standard textbook of cardiolog f il to e n mention them Nevertheless they h e been known to foll w either hem t genous di semin tion of bacteria from dist nt focus or loc l exten ion from b cterial endoc rditis They are aid to be found in from 0 2 to 0 5 per cent of the t t l number of aut psies in a l rge institution F r the most part these bscesses are m ll and recently w h d the opportunit to see a case of multiple m l ry abscesses f the interventricul r septum due to n overwhelmin st phylo cocc l (*Staphylococcu aureus* b cterio ph e type 80 81) pneumonia Sim l rly in bacterial endoc rditi for d a reg tion of pha ocytes in the he rt nd arious or n with or without an soc ted nidus of ne crosis re a c mmon findin 1 9 but l rge myocardi l bsce ses are extremely rare

In the present communic ation we report the occurrence f a large my c rdi l nd hu e plenic absces omplic ting a f t l case of enterococc l endoc rditis The clini cal and p thologic data are discu sed with respect t the p thogenesis of the various manifestations of the disc se

Case report

The patient w a 52 year ol l pur N g o Puert Rican woman wh w admitted t l ne l Hospital w th th omplaint f omiting general ized w kness nd e tri pain th t h d been present for 3 da

The patie t dmitte l t m n m der t rinker f al h l er period f m y y rs S m 1958 he n derw nt t t l g trect my f g tr p j m st my t ther h spital bec use of l er At per t on liver biopsy w performed nd w reported to b m Lae ne irrh sis Since th he had bee symptomatic until 2 t 3 week prior to dmi At that time he first t l generaliz d painles bdominal enla m t which ten led t pr res until the time of dmiss on In the 3 day prior t dmi sion there ha l been repe t l omiting w kness w ll ng of b th leg nores p ri d harp epi astric pain n d b lachr S far k wn there was hi t ry of heart d se se rhe matic fever hort ness f breath h m pty is hest pain or recent hematemesis

Phy l ex mina t on t th time of dmi i n rev l l w ll d lop l Puert R w oma in no d tres The temperature w 99 0 F rectally blood pressure w 130/80 mm Hg f lse w 110 nd regular Resp t on were 22 Sev l pider an omata w re seen th best The scler e were i teric an l th l t ere pal e The lun were lear Card c examination f il l t re l ny murmurs or ther b normalit The bd men w protuberant and it surface showed n rg d uperficial e ord he d l mulli ne cur nd w r The flank were dull t percu ion n l fluid w w d nt f The l of the liv r w palpabl 5 fi ertic ith l t ro the c st l m rg n w t and w firm l t e ler The pleen w n t palp bl There w no peripher l ed ma

At the time of th patient dmi n the bl od cou t he l pan ytopenia with hem gl b n of 7 8 Gm l whit blood ll c unt of 2,400

F om he Medic l Serv e and he Department of P th l gy Mor isania H p t l New York City N Y
Received f publication Jan 17 1961



Fig 1 Cross section through the posterior wall of the left ventricle showing the blood filled myocardial abscess cavity 2.5 cm in diameter. The arrow points to the sinus tract connecting the abscess with the left ventricular chamber. Note that only a thin rim of myocardium separates the abscess from the pericardial space

The differential count was normal. The liver profile indicated hepatocellular damage. The chest x ray film revealed normal cardiac silhouette and normal lung fields. The electrocardiogram was within normal limits

Her protracted hospital course was stormy, complicated and progressively downhill. Shortly after admission she became acutely ill with persistent fever of 100-104 F. A Grade 3 apical systolic murmur appeared and left heart failure supervened. Gradual and progressive enlargement of the spleen occurred. She developed small hematoma of the leg and several subconjunctival hemorrhages, pneumonia, focal seizures with left sided symptoms, left hemiplegia, bilateral cortical d rhythms on the electroencephalogram, progressive anemia, positive stool guaiac, pyuria and hematuria, mild azotemia, intermittent leukopenia and thrombocytopenia and acute left upper quadrant pain. Serial cultures of blood and urine were positive for enterococci. She was treated with massive doses of penicillin and large doses of oxytetracycline, novobiocin, chloramphenicol and streptomycin—alone and in combination—and she became afebrile during the last 6 weeks of her hospitalization. Clinically, though, she continued to deteriorate. Serial electrocardiograms showed only sinus tachycardia and terminally multifocal ventricular premature contraction. On the one hundred and tenth day after admission the patient died

Autopsy The most striking findings on post mortem examination were in the heart and spleen

The heart weighed 400 grams. The pericardium was unremarkable and the pericardial cavity contained only 20 cc of fluid. Grossly the right atrium and tricuspid valve were normal. The right ventricular wall measured 1 cm in thickness. The left atrium was approximately three times normal in size and its wall was thickened. The circumference of the mitral valve (*ring*) narrowed to 8 cm. The mitral leaflets were thickened and sclerosed and their atrial surfaces were partially ulcerated and studded with small vegetations 0.8 cm in diameter. Microscopic sections of the leaflets revealed the changes of an old calcific rheumatic valvulitis with superimposed acute inflammatory elements and bacteria were noted. The capacity of the left ventricular chamber was decreased. The papillary muscles of the left ventricle were hypertrophic and their chordae tendineae were shortened and thickened. The left ventricular wall was thickened to 2.3 cm. A clot of blood was attached to the under surface of the posterior mitral leaflet and pocketed in the pace bounded posteriorly by the posterior ventricular wall, superiorly by the posterior mitral leaflet and anteriorly by the shortened papillary muscles and chordae tendineae. Sectioning through this area showed that this blood clot was continuous with a sinus tract with a blood filled abscess cavity contained within the posterior ventricular wall. This cavity measured 2.5 by 1.5 by 1 cm. Surrounding this large abscess cavity were several small satellite abscesses. Microscopic sections through the myocardium adjacent to the large abscess cavity showed extensive hemorrhage and fibrous and calcified emboli within many of the small branches of the coronary arteries. The remainder of the left ventricle revealed foci of myocardial fibrosis, hyalinization and chronic inflammatory cells. Gram staining of sections throughout the left ventricle frequently showed Gram positive cocci (presumably enterococci) in the areas of bland necrosis. Grossly the coronary arteries, aorta, pulmonary vessels and semilunar valves were unremarkable

The spleen weighed 900 grams. Grossly half of the splenic surface had gray white color and was fluctuant. Sectioning of this area showed a large abscess cavity which measured 11 by 8 by 6 cm and contained 260 cc of fluid pus and 240 grams of solid pus mixed with necrotic splenic pulp. Grossly the remainder of the splenic parenchyma was normal. The hilar portion of the splenic artery was almost completely occluded by a layered blood clot and the vessel wall in this area showed acute endarteritis

The lungs showed hemorrhagic pneumonia, consistent with multiple microscopic infarcts. The right sided pleural effusion of 60



Fig 2 Cross section of the spleen showing the large splenic abscess 11 cm in diameter

Review

The nephrotic syndrome

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Augusta, Ga.

This common but extraordinary condition is known by many names. By older pathologists it was referred to as *chronic parenchymatous nephritis* or the *large white kidney*. In 1913 Munk,[illegible] noting anisotropic fat in the urine of some patients with florid syphilis, called it *lipoid nephrosis*, a name which soon received the endorsement of Volhard and Fahr's famous classification of renal disease. More recently, Ellis' term *Type II nephritis* has been widely used, but the electron microscope has revealed more subtle differences. The terms *lipoid or genuine nephrosis* and *membranous glomerulonephritis* have been used interchangeably to describe the thickening of the glomerular basement membrane so commonly seen even by light microscopy, but some[79] would separate even these two conditions, applying the former term only to those kidneys in which the sole lesion is in the glomerular epithelial cells known as podocytes.

The view is here taken that the noun *nephrosis* should be abandoned in favor of the term *nephrotic syndrome*, which is applied in a loose descriptive sense to all patients with proteinuria, hypoalbuminemia, hyperlipemia, and edema without regard to the renal lesion, although variations are common. Since all such patients thus far appropriately examined have shown changes in some part of the glomerular filter, and since progressive thickening of this membrane so often leads to glomerular hyalinization, the term *membranous glomerulosclerosis* appears to be a reasonably satisfactory way of grouping together the various etiological entities. The nephrotic syndrome thus becomes a constellation of clinical abnormalities which may have many causes. It should be regarded in the same light as such other phenomena as fever, jaundice, anemia, cyanosis, etc. For those reluctant to give up established terms, the idiopathic variety of this sclerosing lesion is synonymous with *lipoid nephrosis*. Until much more is known about the chemistry of renal protoplasm, it seems premature to separate "podocyte disease" from processes involving the basement membrane also. Even the electron microscopists disagree: some emphasize the primacy of the epithelial (podocyte) lesions,[40,41] whereas Spiro[1] describes gaps in the basement membrane through which epithelium and endothelium come in contact, and Movat and McGregor[106] claim that the basement membrane only appears to be thickened because of a layer of extravasated protein beside it. A number of observations suggest that the most common lesion in any disease accompanied by the nephrotic syndrome is swelling and smudging of the foot processes of the epithelial layer of Bowman's membrane and that this change may be reversed by steroid therapy.[41] Thickening of the basement membrane and other glomerular lesions are apparently permanent.

Clinical features. The patient, usually young, swells insidiously and to a degree

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which varies from a trace of puffiness about the face and ankles to the most grotesque dropsy. There is usually nothing in the history to explain the illness, although many give a vague account of "allergy" of one kind or another.[89] Subjective complaints are few, except for a sense of heaviness. The arterial blood pressure is usually normal. Pallor is often striking, but anemia is seldom marked unless the patient is also uremic. Muehrcke[100] has described parallel white lines in the fingernails which he thinks are indicative of hypoalbuminemia, but we have seen them infrequently. Intercurrent infections are frequent; the respiratory tract and the peritoneum are especially vulnerable to hemolytic streptococci and pneumococci, and these infections are often accompanied by bacteremia which may not be transient. This susceptibility to infection may be related to the low gamma-globulin content of the serum and to consequent lack of antibody formation. Spontaneous remissions occur,[23] sometimes during convalescence from such contagious diseases as measles or chicken pox, but relapses are common. In such patients the appetite is poor and a very large loss of tissue mass may be masked by the edematous fluid. If the renal lesion does not heal, the kidney eventually shrinks, the blood pressure rises, and symptoms associated with the uremic syndrome appear. It is commonly said that the nephrotic syndrome disappears as renal failure advances because contracted kidneys excrete less protein, but most patients with hypertension and uremia due to disease of the basement membrane remain somewhat edematous to the end, partly no doubt because of heart failure and anemia. A few, however, never have edema at any stage of the disease, and in them the diagnosis can only be suspected from the magnitude of the proteinuria and the presence of oval fat bodies in the urine. There is no evidence that these so-called "dry nephrotics" have a better prognosis than do those with edema.

Pathogenesis

Edema. From the patient's viewpoint dropsy is the most conspicuous feature of this fascinating disorder, but it is important to note that profound disturbances in the metabolism of protein, fat, and electrolytes also occur. Although it is an extraordinary thing that *an organism should find it necessary* to enlarge itself with brine, the physician who limits his therapy to measures designed solely to increase the flow of urine is taking much too small a view of the problem. Indeed it is probable that the retention of salt water may even serve a useful purpose. The circulation may be unable to meet the metabolic needs of the body, either because the cardiac output is too low or because the blood volume is too small. The renal tubule responds to these stimuli by resorbing sodium and water at an accelerated rate. The cardiac output is normal in patients with the nephrotic syndrome unless heart failure coexists or blood volume shrinks greatly, but the best measurements indicate that hypovolemia, perhaps only in some critical part of the vascular tree, is a common and possibly an essential feature.[*] Hypoproteinemia from any cause lowers oncotic pressure. The chief force which holds water inside the capillary bed is the osmotic pressure of plasma proteins; when this is reduced, water tends to move to an extravascular position and blood volume falls. If protein depletion continues, this shrinkage may lead to critical drops in blood pressure and flow, which in turn produce antinaturesis and antidiuresis by reflex mechanisms integrated in the hypothalamus.† There is evidence that secretion of aldosterone is controlled by a glomerulotrophic hormone from the posterior diencephalon. Saline is returned to the body by the renal tubules in an effort to counterbalance the falling blood volume, but since plasma oncotic pressure is low because of hypoproteinemia, the fluid cannot stay within the capillary bed and passes outward to interstitial spaces. Bloomer suggests that the formation of both aldosterone and ADH are increased as integral parts of the neph

Leutscher[88] [illegible]

†I [illegible]

rotic syndrome[83] but there are many patients—the so called *dry nephrotics*—whose hypovolemia is presumably too slight to produce edema. Even though it is always pleasant to watch a nephrotic patient diurese the physician must constantly fix his attention upon that metabolic dysfunction which is more important than edema and probably the most fundamental cause thereof—hypoproteinemia.

Hypoproteinemia. The depletion of protein which is so characteristic of the nephrotic syndrome can be due to (a) diminished formation, (b) increased excretion, (c) increased destruction, or (d) any combination of these three possibilities. There are no good reasons for believing that synthesis of plasma proteins is defective; on the contrary, hypoproteinemia is a potent stimulus to this process. Available studies indicate that the formation of protein is at least normal.[19] Most patients are eating well when the syndrome appears and few have any demonstrable liver disease. There is, on the other hand, no doubt that chronic proteinuria makes demands upon stores of protein which may not be met indefinitely. Squire[140,158] believes that external loss is the chief reason for the hypoproteinemia, but it is often difficult to detect any consistent correlation between the amount of protein in the urine and the lack of it in the serum. It is difficult to resist the idea that increased protein catabolism may be an important factor. The volume of glomerular filtrate is so large (approximately 180 liters per day) and the concentration of albumin so appreciable (150 mg. per liter) that a considerable amount of albumin (27 Gm.) must of necessity be resorbed by the tubules. In addition, a large quantity of nonprotein nitrogen is also filtered and resorbed and is thus available for metabolic purposes. Even slight defects in the tubular transport mechanisms may thus in time account for very large deficits of protein. If, for example, none of the filtered albumin were returned to the blood stream as such, the daily deficit would be about 30 Gm., a much larger amount than that usually lost in the urine by the nephrotic patient and a close approximation to the 0.25 Gm. of serum albumin per kilogram of body weight formed daily by the normal adult.[149] One might expect to find that renal venous blood contains less serum albumin and more nonprotein nitrogen than does other venous blood in comparison with simultaneous arterial analyses, and several groups have found this to be the case.[87] Conflicting evidence acquired by perfusing rat kidney with I^{131} albumin exists, however.[144] In addition, Harms[66] has shown that these arteriovenous differences are accentuated in rats with antikidney serum nephritis and he has furthermore shown that the proteolytic activity of such kidneys is definitely greater than normal. Gitlin and colleagues[60,61] and Kaitz[7] reported that radioactive protein given intravenously disappeared from the blood stream of nephrotic patients much more rapidly than from the circulation of normal subjects. Freeman and Mathews[52] reported that the nephrotic patient differs from the normal person in that albumin catabolism is increased as a fraction of the intravascular pool but decreased as grams per day. Conflicting data on patients with idiopathic hypoalbuminemia suggest either that protein is catabolized somewhere at an excessive rate or that it is lost in the stools.[8,129,14,158] I^{131} labeled albumin disappeared from the blood stream of mice much more slowly if both ureters were ligated or both kidneys removed. Although Chinard's calculations indicate that proteinuria is due to glomerular disease,[3] decreased tubular resorption may also be a factor[158] and the beneficial effects of adrenocortical steroids in the nephrotic syndrome may be attributed not only to their action upon capillary permeability but to a possible normalizing effect upon the tubular transportation of nitrogenous compounds.[44]

Lipemia. Although a rough inverse relationship exists between the serum concentrations of albumin and fat in the nephrotic syndrome, there are nonrenal diseases (cirrhosis of the liver, starvation, for example) in which no such correlation exists.[73] The metabolism of lipoproteins is a new and difficult field but several generalizations of clinical importance have emerged from accumulated evidence.[164,4]

A. Lipids become water soluble only when linked with plasma proteins. About two thirds of the total plasma lipid is normally contained in the beta lipoprotein

fraction the alpha globulins carry the remainder. In the nephrotic syndrome all lipid fractions are increased, neutral fat most of all and cholesterol more than the triglycerides and the phospholipids. Lactescence of nephrotic serum is determined by the relative amount of low-density (Sf 10-200) lipoprotein molecules; patients with the least amount of circulating albumin and the most edema are apt to have the creamiest sera. Those with milder varieties of the condition who have clear serum have hyperbetalipoproteinemia with high-density (Sf 3-9) molecules predominating.

In normal subjects lipoprotein synthesis seems to begin in the low density range, the molecules of which convert to the high-density type with the transfer of lipid to albumin molecules. In the nephrotic syndrome this conversion is inhibited for unknown reasons so that Sf 10-200 complexes accumulate. Conversion is facilitated (and lipemia combated) by infusions of albumin or by transplantation of the ureters of nephrotic animals to their own great veins to prevent loss of albumin.[10] Numerous studies indicate that the turnover rates of lipids and lipoproteins are prolonged in nephrotic animals and man.[9, 11] Consistent abnormalities in lipoprotein lipase activity have not been demonstrated. The role of the "lipid mobilizing factor" has not yet been clearly established, but heparin has marked ability to remove the Sf 10-200 molecules very rapidly from the serum of some nephrotic patients. The accumulation of lipids in serum has been likened to a "traffic jam" occasioned by the circumstance that by one means or another protein is disposed of more rapidly than is fat.

Increased permeability of Bowman's membrane leads to disproportionate loss from the serum of the smaller protein molecules (albumin, alpha globulin, ceruloplasmin, transferrin, etc.). Predominance of the larger complexes results (alpha 2 globulin, beta globulin, fibrinogen).

Other laboratory abnormalities. The mystery of the nephrotic syndrome lies in the fact that the urine contains *too much* protein, the serum too little. If electrophoretic patterns of the two fluids are compared, one is seen to be the rough inverse image of the other, particularly in regard to the albumin contained in each. There is a vague positive correlation between the intensity of the proteinuria and the severity of the hypoproteinemia, but patients who excrete 30 Gm. of protein daily (mostly albumin) often have a concentration of serum albumin no lower than that of those who have much lower excretion rates of albumin. *Proteinuria greater than 3.5 mg. per day is* rare in other diseases.[13] The concentration of serum albumin is commonly reduced to about 1.0 Gm. per cent, but virtual analbuminemia has been seen. Serum cholesterol may be in excess of 1.0 Gm. per cent.

The blood count is normal in the early stages, although the hematocrit may be a little high because of hypovolemia. When renal insufficiency appears, a normochromic and normocytic anemia is usually found, due possibly to erythropoietin deficiency. Hypoferremia and hypocupremia have been reported,[4] probably because metal-binding proteins are lost in the urine. The serum PBI is also often low because of the inability of plasma proteins to bind normal amounts of organic iodine,[1, 12] but the rate of uptake of radioiodine is normal. Despite a low basal metabolic rate there is no evidence of hypothyroidism. The thyroid responds normally to TSH and desiccated thyroid. The titer of antistreptolysin-O in the serum is usually low, in contrast to the increase so commonly seen in proliferative glomerulonephritis; circulating complement is also reduced.[14]

Gross hematuria is rare, but showers of red cells may appear in the urine from time to time. Leukocytes, epithelial cells, and casts are surprisingly scanty. The important diagnostic clues are: (1) the presence of *oval fat bodies*, large epithelial cells full of fat droplets which are stainable with Sudan III, or which can be seen with polarized light as doubly refractile Maltese crosses, and (2) heavy proteinuria, an amount in excess of 3.5 Gm. per day being highly suggestive.[13] Urinary protein is chiefly albumin, chemically and immunologically identical with normal serum albumin. Heavy globulinuria has been regarded as a bad prognostic sign,[4, 7] but this has been denied by others.

Renal function. The nephrotic syndrome often appears in patients whose renal func-

tion is entirely normal even when tested by refined clearance and saturation techniques; indeed, many have abnormally high rates of renal blood flow and glomerular filtration. Later reduction of these values bespeaks glomerular fibrosis, arteriolosclerosis, or infection. Tubular dysfunction is evident in many ways. Occasional patients excrete small amounts of glucose and/or amino acids.[u] Since many nephrotic subjects have relatively normal glomerular filtration rates and serum electrolyte concentrations, it is certain that their edema is of tubular origin. The mere presence of edema is *prima facie* evidence that the kidney is excreting less sodium than the blood brings to it, and the fact that the serum is often hyponatremic is evidence that water is retained more tenaciously than salt. Conceivably the proximal convolution can resorb isotonic fluid at an increased rate, but there is no evidence that this occurs as an isolated phenomenon. Little is known about the impact of disease upon the concentrating and diluting mechanisms of the loop of Henle, but the forces making for countercurrent diffusion may in some obscure way become so distorted as to intensify the resorption of water by the collecting ducts. Efforts have been made to find a common basis for the disturbances in renal handling of protein, salt, and water. It has been suggested, e.g., that the increased rate of protein catabolism liberates potassium which the kidney must excrete and that retention of sodium occurs in a compensatory manner, but the losses of nitrogen and potassium are not always proportional.[86] Abnormal permeability of cell membranes to the transfer of Na, K+ and protein may be of adrenocortical origin.[84] Metcoff et al. showed that the nephrotic kidney responds to Diamox and to a nonresorbable anion (PAH) by excreting far more K+ than does the normal kidney, possibly because of intense concentration of sodium; they also showed that the nephrotic kidney can secrete hydrogen even under the influence of carbonic acid inhibitors, whereas the normal kidney cannot.

The nature of the renal lesion

For many years internists have regarded patients with the nephrotic syndrome as atypical examples of glomerulonephritis despite the fact that hematuria, hypertension, and unequivocal evidence of antecedent streptococcal infection are often conspicuously absent. It was assumed, therefore, that the initial episode had been overlooked or forgotten, but pediatricians have long been inclined to believe that the two disorders are unrelated, the strongest arguments being that the nephrotic syndrome often appears in children who on an average are distinctly younger than those in whom acute hemorrhagic nephritis of the post-streptococcal variety usually occurs, and that serological evidence of bacterial infection is seldom found in the nephrotic syndrome. Longcope[87] pointed out that the clinical course in patients suffering from acute hemorrhagic glomerulonephritis (Type A) differs in many respects from that seen in patients suffering from the nephrotic syndrome (Type B), and later Ellis[1] renamed these groups Types I and II. Clinicians are now generally inclined to the view that the renal response to infection with certain strains of beta hemolytic streptococci carries a relatively good prognosis, but that most patients whose illness begins with the nephrotic syndrome die of renal failure. Experimental evidence, however, suggests that the same agent may under different circumstances cause either epithelial proliferation or simple thickening of the basement membrane. Mixed lesions are commonly found in human kidneys. The view is here taken that certain strains of beta hemolytic streptococci are only one of many different agents capable, under appropriate conditions, of causing the membranous changes so characteristic of the nephrotic syndrome. Glomerulosclerosis, then, is due to many factors but is all too often idiopathic (for this group *genuine* or lipoid *nephrosis* are the conventional names but in our opinion less satisfactory ones). A considerable proportion of patients give a history which suggests hypersensitivity reactions.[85] Bacteria other than streptococci have evoked the disease, and it is possible that viruses may do so also.

Bell was evidently the first to apply the term *membranous glomerulonephritis* to this lesion, but he expressed uncertainty as to whether it was related to antecedent

streptococcal infection or not. In splendid reviews both Allen[4] and Ehrich[39] have accepted this dual concept and emphasized its importance. In early stages the glomerular capillaries are widely patent and there is none of the endothelial proliferation and intracapillary thrombosis so characteristic of post streptococcal disease. Later, when hyalinization and fibrosis have destroyed all glomerular landmarks, it may be impossible to distinguish between the two varieties. Some kidneys show both sclerotic and exudative changes. If hypertension has existed for any length of time, arterial and arteriolar sclerosis are found, and necrotizing vasculitis suggests the clinical picture of malignant hypertension. The tubular changes, once thought to be of primary importance, are now regarded merely as visible evidence of the fact that the glomerular filtrate contains more fat and protein than the tubules can comfortably deal with. The proximal convolutions especially and to a lesser degree the straight segments and the distal convolutions contain such large quantities of lipoprotein in droplet form that the epithelial cells themselves are often swollen and flattened; the droplets stain with Sudan III and the esterified cholesterol in them reveals itself under polarized light as the well known but infrequently searched for doubly refractile lipoid bodies. The collecting tubules are not often involved. Hyaline, granular and fatty casts lie in the tubule lumens. The whole kidney may have a soft, yellowish grey look, but in later stages atrophy of some nephrons, hypertrophy of others and overgrowth of connective tissue make for a small rough organ. As the number of functioning nephrons diminishes, the amount of protein and formed elements in the urine naturally decrease also. Gross hematuria is apt to result from arteriolar necrosis.

A small proportion of nephrotic subjects shows no glomerular lesions in tissue sections examined by light microscopy, but the electron microscope demonstrates changes in the glomerular basement membrane and especially in the podocytes.[43, 44, 46, 47] The earliest and apparently the most specific lesion consists of a swelling of the epithelial cells of Bowman's capsule and of coalescence of their foot processes; this seems to antedate the proteinuria and somehow to be responsible for it. The lesion is a reversible one which disappears during clinical remissions.[46] The splitting and thickening of the basement membrane so regularly seen regardless of etiology is likely to be permanent and to progress to complete glomerular hyalinization. Hence the term *glomerulosclerosis* seems apt. It should be pointed out, however, that the tubular epithelial cell and the podocytes are embryologically identical and that both rest upon a common basement membrane; disease in the glomeruli therefore bespeaks disease in the convoluted tubules, and leakage of protein into the urine may correlate with disordered tubular transport of protein. No pathognomonic tubular lesions have been described but they may be obscured by the masses of lipoprotein droplets which so often fill the epithelial cells of the nephron.

In elaborating on the varieties of renal disease, much reliance is placed upon the extensive biopsy experience of Kark and his colleagues.[73] Their paper contains an authoritative bibliography also.

Common causes of the nephrotic syndrome

I. Glomerulonephritis. Clinical tradition supports the belief that a small proportion (10 to 15 per cent) of patients with acute glomerulonephritis of the hemorrhagic and proliferative type pass through a phase of nephrotic edema on their way to total renal failure.[81]

II. Glomerulosclerosis.

1. IDIOPATHIC. Since the lesion is occasionally seen in newborn infants,[41] the responsible agent(s) must pass through the placental barrier; it has been suggested that the mother may produce antibodies against the fetal kidney. The etiology of the postnatal variety is unknown but there is circumstantial evidence which suggests that immune reactions may be responsible. External agents are theoretically able so to modify renal proteins or mucopolysaccharides that they become antigenic; fixation of the autoantibody in glomerular basement membrane then produces the lesion. This theory of autoimmunization is attractive but unproved.

2. METABOLIC. (a) Diabetes mellitus.

(b) disseminated lupus erythematosus (c) amyloidosis (d) myelomatosis (e) eclampsia

3 INFECTIOUS (a) hemolytic streptococci (b) other bacteria (c) syphilis (d) quartan malaria

4 CHEMICAL (a) heavy metals (bismuth gold mercury particularly) (b) anticonvulsant drugs (trimethadione paramethadione tridion particularly) (c) bee or wasp venom (d) poison oak poison ivy (e) pollens (f) serum

5 CONGESTIVE (a) thrombosis of renal vein (b) constrictive pericarditis

6 MISCELLANEOUS Polyarteritis nodosa Henoch Schonlein purpura sickle cell disease pyelonephritis and arteriosclerosis have been described but the association may be fortuitous

The experimental counterparts

I Antikidney serum nephritis (AKS) Although certain strains of group A streptococci (types 12 18 and 25 particularly) are the most frequent cause of proliferative glomerulonephritis in man attempts to reproduce the disease in animals by injecting them with nephritogenic strains succeed only occasionally [104] Although others had worked with AKS before him (Lindemann 1900 and Pearce 1904) it was Masugi who showed in 1933 that something very much like the human disease could be produced with it [97] His technique is in all essentials still the standard one in use today The serum is made by injecting crude saline extracts of kidney from one species (often the rat) into another species (often the rabbit) either intramuscularly or intraperitoneally after an interval which permits maximal formation of antibodies the recipient animal is bled and its serum injected back into fresh animals of the first species On the basis of the potency of the serum and other factors not well understood these animals soon develop proteinuria hypoproteinemia edema hypertension lipemia and azotemia to a variable degree The resulting picture is therefore a mixture of nephritis and nephrosis The evidence shows that the rat is more likely to develop the nephrotic syndrome than the dog which usually becomes uremic Complete recovery by either species is possible but death from uremia in a few months is more common [44, 76]

Seegal and Bevans[19] summarize in detail the pathologic and clinical changes During the first month of the disease the clinical picture corresponds to that seen in acute proliferative glomerulonephritis in human beings the first visible renal lesion is swelling of the glomerular basement membrane and this is quickly followed by proliferation of capillary endothelium thrombosis and necrosis of the glomerular tufts cellular infiltration of the glomerulus and a leakage of fibrin and red cells into Bowman s capsule The tubule cells are swollen and often desquamated and many casts are seen within the tubule lumens If the animal survives the first month the proliferative and exudative reactions subside but the basement membrane thickens and the intraglomerular capillaries thrombose With the passage of time glomeruli become entirely obliterated and can be recognized as fibrous balls containing varying amounts of hyaline material Basement membranes become progressively thicker and fat infiltrates the tubular epithelial cells The nephrotic syndrome may appear either early or late and it may disappear spontaneously The electron microscope shows that an osmophilic exudate very quickly appears between the layers of Bowman s membrane in AKS treated mice and rats and that this is followed by swelling of the pedicels and thickening of capillary epithelium [118, 134] a reaction which could represent fixation of antibodies These structural changes are accompanied by histochemical evidence of alterations in the activity of certain hydrolytic and oxidative enzyme systems [106] Studies of human material at the University of Minnesota were probably the first which showed the constancy of the podocytic lesions in various types of nephrotic children [41, 144] and similar changes have been described by Kark s group in Chicago [44] Excessive amounts of globulin (antibody ?) in the glomeruli and around the tubules of patients with a wide variety of kidney diseases have been found by means of the fluorescein staining technique [41, 94, 96, 138] but the meaning of this is unclear Krakower and his colleagues [42, 44] have presented evidence that the glomerular basement membrane is the most potent source of antigen and a number of laboratories

have shown that labeled globulins concentrate most intensely in the glomeruli,[?] possibly because of the enormous quantity of blood which normally irrigates these structures. The problems are extremely complex, however, because both the kidney extracts and their antisera are obviously impure. A common antigen probably occurs in many tissues. Any interpretation of this phenomenon must recognize the fact that there is usually a latent period of a few days between the injection of AKS and the appearance of renal disease. The lesions may not be due to fixation of renal antibodies, therefore, but to the fixation of antibodies evoked in the rat against the injected serum of the rabbit[?] or to a gamma globulin in it.[?] Further intricacies arise from the fact that the union of antigen and antibody may so alter the gamma globulin molecules involved that the new complex itself becomes antigenic and able to invoke its own immune response; theoretically, at least, this process of continued protein denaturation and autoimmunization could go on indefinitely. Human renal disease has been explained analogously by the supposition that many foreign substances—streptococcal products, for example —may so alter the renal proteins of susceptible individuals as to make them antigenic, but no one has consistently found renal antibodies in the serum of patients with kidney disease. Since adrenocortical steroids modify immune reactions, it may be important to note that Goodman and associates[?] found that renal tubular epithelial cells and glomerular epithelial cells have antigens in common. Nephrotic rat kidney has increased proteolytic activity[?] and enzymes may themselves be antigenic.[?] It should also be noted that not many workers have used true autoantibodies; although they have often called them such, they have usually used homoantibodies instead, so that there is some question of a foreign protein reaction within the same species. Heymann is one of the few who has attempted to produce nephritis in uninephrectomized rats with preparations made from the animal's own excised kidney; he found that a mixture of kidney protein and Freund's adjuvant is an effective agent.[?]

II. Chemical nephritis

1. AMINONUCLEOSIDE. Metcoff and colleagues[?] first reported that a derivative of the antibiotic *puromycin* can produce the nephrotic syndrome in animals. The active substance (3, 6-dimethylamino purine 3-amino D-ribose) is made by removing a molecule of tyrosine from a molecule of Puromycin. It is evidently not a simple protoplasmic poison because there is a definite latent period between the time of administration and the appearance of proteinuria, even after intravenous injection. Thickening of the foot processes and the basement membranes occurs, and chronic renal disease can be produced by repeated administration, but the syndrome is reversible. Recant and colleagues reported that the earliest changes detectable by the electron microscope were in the podocytes[?] and that these changes were associated with inhibition of the formation of ATP, suggesting abnormalities in nucleoprotein metabolism[?] as a factor in the disease in rats. Hartman reviewed her work and that of others which indicates that the glomerular lesion may be due to an antimetabolite resembling adenosine. No evidence of antibody formation has yet been found. Harms[?] found that slices of tissue from such kidneys exhibited increases in catheptic activity similar to those shown by slices from AKS-treated animals.

Corticosteroids have an uncertain ameliorating effect upon nephropathy due to AKS and none upon that due to aminonucleoside.

2. TRIDIONE. A few epileptics have become edematous while taking certain anticonvulsant drugs, and rats given large doses of Tridione for many months have developed glomerulosclerosis and proteinuria but no edema.[?]

3. IRON OXIDE. Saccharated iron oxide has produced a similar syndrome in rabbits.

Differential diagnoses

Recognition of the nephrotic syndrome is no problem even in the absence of edema if a heavy, continuous proteinuria prompts the physician to look for the characteristic changes in urine and blood. The real difficulty comes only too often when he tries

to find the cause and from its detection to say something about treatment and prognosis.

As in other areas the history is all important, particularly as to contact with mercury in the form of diuretics[3] or teething powder, bismuth, bee venom,[136] poison oak,[137] poison ivy,[?] and anticonvulsant drugs.[139] Serum, pollens, trichorethylene, and gold have also been implicated, and the syndrome has occurred during such infectious disorders as quartan malaria, secondary syphilis, diphtheria, and subacute bacterial endocarditis. A very small number of nephrotic adults give a history of acute hemorrhagic glomerulonephritis, a disease also uncommon in children under 5 years of age. When the fact is considered that the average American child has four or five colds per year, it is difficult to relate ordinary infections of the respiratory tract to the appearance of edema. Bloom and Seegal found that about half of their patients who died of renal failure had passed through a nephrotic phase, but that neither pyelonephritis nor renal arteriolosclerosis bore any causal relationship to the nephrotic syndrome, a fortunate circumstance which simplifies the diagnostic difficulties appreciably.

Renal function tests of even the most refined nature measure the *extent* of disease rather than its *kind* and give no prognostic aid at all unless repeated at enough intervals to afford some estimate of the tempo of the process. Intense proteinuria is characteristic of all varieties of the nephrotic syndrome and may be massive in patients whose glomeruli show minimal disease. Red cells are usually scarce but gross hematuria occurs at times. In the early stages, casts, hyaline or granular, may be surprisingly rare. The important element in urinary sediment is the *fat body*, deposits of cholesterol esters in leukocytes, epithelial cells or casts which show up so well in polarized light as doubly refractile Maltese crosses. These are not pathognomonic for the nephrotic syndrome but are more numerous in hyperlipemic states.[138] Pyuria is seen in noninfectious lesions such as lupus erythematosus, so that the appearance of excessive numbers of leukocytes and glitter cells, even in clumps, should not be equated with bacterial disease. Bacteria in casts, however, give certain evidence of renal infection. The broad casts of renal failure are more often seen in the urine of patients who also have azotemia and hypertension. Schreiner has recognized a wide spectrum of formed elements in the urine of patients with the collagen diseases.[10]

The introduction of paper electrophoresis about 1950 was a major advance beyond the older chemical techniques for estimating albumin-globulin ratios, but the significance of the variable globulin patterns in the sera of patients with renal diseases is not yet clear. The proteins which escape most easily into the urine (alpha globulin, gamma globulin, transferrin, ceruloplasmin, albumin) are those whose molecular weights are less than 200,000, and these are apt to be scarce in the plasma.[10] The larger molecules are excreted with more difficulty, so that the concentrations of alpha[2] globulin, beta lipoprotein, and fibrinogen in serum are usually high. Since the urine of nephrotic patients is essentially fat free, some dissociation of lipoproteins probably takes place in the kidney, but we, like others, have been unable to detect any useful correlation between the globulin partition pattern and the structural changes in the kidney except that an increased amount of gamma globulin is more commonly found when the nephrotic syndrome is due to some systemic disease, such as lupus erythematosus, rather than to simple glomerulosclerosis. Lipoproteins are often abnormal, moving between the α and β peaks of normal serum.[83]

Renal biopsy. Since treatment and hence prognosis depend upon precise diagnosis, needle biopsy of the kidney is often a justifiable procedure, particularly among young patients who are neither hypertensive nor uremic. Large numbers of biopsies on nephrotic patients have been reported from Scandinavia,[1] England,[77] Washington,[14] and Chicago.[78] The wide variety of lesions found in the 98 cases so studied by Kark[78] is impressive. Only about one half of these cases were diagnosed pathologically as some sort of glomerulonephritis (usually membranous but sometimes proliferative or both); 18 patients had lupus erythematosus, 15 were diabetics, 3 had

amyloidosis and in 11 the only glomerular lesions were in the podocytes. The importance of this lesion is its reversibility by hormonal therapy,[17 3 44 46] whereas the renal lesions which accompany such metabolic disorders as diabetes mellitus, disseminated lupus erythematosus or amyloidosis are notoriously refractory to steroid treatment. The decision to perform a biopsy or not must be made in each case on its own merits, for some danger attends even in the hands of experts.

Associated diseases

It is not enough to arrive at a diagnosis of the nephrotic syndrome. Effort must be made to identify associated disorders which are frequent and sometimes curable.

Chronic proliferative glomerulonephritis. In acute glomerulonephritis of streptococcal origin, electron microscopy shows, as anticipated, marked edema of both the endothelial and epithelial components of Bowman's membrane, together with an accumulation of basement membrane-like material between the proliferating endothelial cells; it is this which obliterates glomeruli in chronic disease, but changes in the podocytes are minimal.[1]

Disseminated lupus erythematosus. A valuable three-dimensional view of the natural history of lupus nephropathy is afforded by Kark's extensive biopsy studies.[37] These suggest that nearly all patients who live long enough will exhibit the nephrotic syndrome, and of course uremia is a common terminal event. The disease begins in the glomerular capillaries with an irregular focal thickening of the basement membrane. Adjacent endothelial cells proliferate and deposition of fibrinoid within the capillary walls gives to it a smudgy eosinophilic appearance. Wire-loop lesions are simply focal collections of fibrinoid. Hematoxylin bodies, hyaline thrombi and glomerular sclerosis develop later, if at all. It is the combination of lesions rather than the appearance of any one of them which establishes the diagnosis. Systemic evidence of lupus often subsides as renal failure proceeds, in which event the urinary sediment may offer an important diagnostic clue. Krupp[37] showed that in patients with lupus and polyarteritis nodosa the urine often contains formed elements of great variety: red blood cells and red cell casts suggest the existence of acute glomerulitis, oval fat bodies, hyaline casts and heavy proteinuria are hallmarks of the nephrotic syndrome, and broad casts from the ducts of Bellini usually indicate renal failure. Schreiner[46] has emphasized the importance of these "telescoped" urinary sediments but warns that they are not entirely specific. Renal biopsy is a particularly useful procedure because the prognosis in lupus nephritis is much more serious than in membranous glomerulosclerosis.

Diabetes mellitus. In 1936 Kimmelstiel and Wilson described *nodular* deposits of a hyaline material in the peripheral portion of glomeruli of patients with chronic diabetes mellitus. Twenty years later Kimmelstiel[16] reaffirmed the specificity of this lesion and described similar deposits in the parietal layer of Bowman's membrane and the basement membrane of tubular epithelium. He agreed with Bell,[3] however, that *diffuse* glomerulosclerosis is a much more common lesion and the one related to edema and hypertension. From a large biopsy experience Kark's group[48] concluded that the nodular variety is never found in the absence of the diffuse lesion and that it correlates poorly with the clinical signs of diabetic nephropathy. They point out that technically this is not a sclerosing lesion but one which is due to the deposition of mucopolysaccharides, a reflection of the underlying metabolic disturbances. The term "intercapillary glomerulosclerosis" should be abandoned, for the electron microscope shows that the essential lesion consists of thickening of the capillary basement membrane together with deposition of mucoprotein within the endothelial cells, although others[31] found the hyaline deposits between the endothelial cells. The diabetes is often so mild that a glucose tolerance test may be necessary to establish its coexistence.[7 48] The presence of oval fat bodies in the urine and of capillary aneurysms in the retina are important diagnostic aids, since nephrosclerosis and pyelonephritis are also common in diabetes mellitus.[46] Effective prophylaxis or treatment do not exist.

Amyloid. In primary amyloidosis

normal proteins are irregularly deposited in the basement membranes of the glomeruli and tubules and in the walls of small arteries, and the glomerular epithelium is also diseased in a spotty, irregular manner.[101, 141] Movat's studies[98] with the electron microscope on human biopsy material showed deposition of amyloid on both sides of an intact basement membrane, together with fusion or destruction of the podocytes. Amyloidosis secondary to myeloma and chronic infection is distributed similarly.[14] Biopsy is the only reliable way of making the diagnosis of either variety, and it is important that it be made, since amyloidosis does not respond to treatment.

Pregnancy. Thickening of the basement membrane with deposition of fibrinoid material on the endothelial side are commonly found in pregnant women with hypertensive cardiorenal disease, but the specific lesion of eclampsia is swelling of the capillary endothelium.[11, 141, 41] This is entirely reversible, but the other changes are not. Disease of the podocytes does not occur. It has been suggested that true eclampsia is due to the fact that mother and fetus are antigenically incompatible in the sense that the mother's blood contains a protein which the child does not have and which therefore produces antibodies to it through the placental circulation—a sort of Masugi experiment in reverse.[11] This theory is unproved but can account for the fact that the mother gets kidney disease but the child does not. In any event, pure eclampsia leaves no residual renal damage.

Venous congestion of the kidney. Chronic congestive heart failure from any cause, and constrictive pericarditis in particular, is occasionally associated with massive proteinuria and its sequelae; in the latter situation, pericardiectomy has been curative.[6, 17] Podocyte disease has been seen.[141] Bilateral thrombosis of the renal veins is a fairly common complication of inferior vena caval thrombosis[17, 118] and may be suspected after physical examination alone. When no signs of caval obstruction coexist, its detection may require an attempt to fill the renal veins with radiopaque material during a Valsalva maneuver. Spontaneous thrombosis of the small interlobular veins also occurs in the course of various renal diseases, but this is a diagnosis which only the pathologist can make. Massive infarction of the kidney due to venous thrombosis happening so quickly that collateral circulation cannot form occurs, especially in children. The clinical picture is usually that of acute renal failure. It is well to remember that the normal renal blood flow is about one fourth of cardiac output.

Other diseases. The nephrotic syndrome has been seen occasionally in polyarteritis nodosa, multiple myeloma, Henoch-Schönlein's purpura, sickle cell anemia, and arteriolar nephrosclerosis,[79] but these examples are so rare as to raise the question of random coexistence.

Treatment

Since *edema* is usually the most striking abnormality, both the patient and his physician may easily become so preoccupied with its control that the more fundamental disturbances are neglected. Anasarca, however, is largely a cosmetic problem, and there is no evidence that the "dry" nephrotic is better off than the "wet" one, although he may have less mechanical discomfort. The therapeutic target should be the abolition of proteinuria rather than the promotion of the flow of urine. If the renal lesion cannot be resolved, however, it is the physician's next duty to maintain optimal nutrition, to prevent intercurrent infection, and to manage the erosions of cardiorenal function as they inevitably appear.

Diuretics. Bed rest for a time and moderate restriction of the intake of salt often reduce edema quite appreciably, even in the face of persistent hypoalbuminemia. Xanthines, mercurials, and carbonic anhydrase inhibitors are less popular than they were before the introduction of the thiazide and phthalimidine derivatives. In such a rapidly expanding field as this, any recommendation can have only temporary validity, but at the time of this writing the following compounds are widely used: chlorothiazide (Diuril), hydrochlorothiazide (Esidrex, Hydrodiuril, Oretic), trichlormethiazide (Naqua), methylchlorothiazide (Enduron), flumethiazide (Ademol), hydroflumethiazide (Saluron), benzydroflumethiazide (Naturetin), and chlorthali

done (Hygroton). We[illegible] among many others have obtained satisfactory responses to 50 mg. of hydrochlorothiazide twice daily and prefer it to mercurial compounds since it induces parallel increases in the output of sodium and chlorides without inordinate loss of potassium. In addition to hypokalemia with its attendant muscular weakness and cardiac arrhythmias, thiazide derivatives may cause hypochloremic alkalosis, hyponatremia, and hyperuricemia with or without clinical gout.[illegible] They have on occasion also produced bone marrow depression, jaundice, vomiting, and dermatitis.

Nephrotic patients react less dramatically on the whole, however, than do patients with congestive heart failure. Steroids which block the action of aldosterone at the renal level (spironolactones such as Aldactone) may be used in conjunction with the above-mentioned diuretics in order to intensify the rate of sodium excretion, and prednisolone may also be added if the patient is hyponatremic as well. Rigorous restriction of the intake of sodium, especially if augmented by cation exchange resins, is apt to accentuate the hyponatremia so regularly seen anyway. Hypertonic saline only increases blood volume and aggravates the edema.

Plasma volume expanders. These materials have been more useful as physiologic tools than as therapeutic agents, but in selected instances may usefully potentiate the actions of steroids and diuretic drugs alike. Human albumin is expensive and much of it is promptly excreted in the urine.[illegible] Plasma substitutes are cheaper and equally effective[73] but have inherent drawbacks of their own. Acacia, widely used for a time, was abandoned when deposits were found in the liver long after administration. Dextran and polyvinylpyrrolidone have been criticized on the same grounds,[illegible] and the former particularly has caused allergic reactions, renal damage, and abnormal bleeding. All substitutes for the patient's own plasma proteins will be effective only when his capillaries are tight enough to permit what Armstrong has called an "iso-osmotic" response characterized by hemodilution. Human blood and its derivatives are all subject to viral contamination, and the physician must balance the temporary benefit accruing from the use of substitutes against their small but measurable toxic properties.

Other agents. Occasionally diuresis has followed the deliberate induction of measles[74] and malaria[4] and short courses of nitrogen mustard.[13] The rationale for their use is tenuous and their real value very much in doubt. Intravenous calcium gluconate may be a mildly useful adjunct to steroid therapy by an unknown mechanism.[illegible] Desiccated thyroid was once administered because the basal metabolic rate is low and the serum lipids high in nephrotic patients, but nephrotic patients tolerate large doses of this material without apparent harm or benefit. Heparin has also been used because of its capacity to disburse blood lipids, but this is yet in the experimental stage.

Hormones. ACTH and adrenocortical steroids are by common consent the only agents which can suppress the disease and prolong life.[illegible] The modus operandi of these substances is unknown, but their diuretic properties must be due to an increase in glomerular filtration rate relative to the rate of tubular resorption of sodium, whereas the abatement of proteinuria may be attributed in part to their anti-inflammatory effects upon the glomerular filter but in greater part to poorly understood metabolic processes. For example, ACTH increases the tubular transportation not only of uric acid and phosphorus but of ammonia and hydrogen too, so it evidently participates in important enzymatic reactions.[illegible] No unifying concept has yet been evolved which satisfactorily coordinates these apparently dissimilar actions. About all that one can say at present is that diuresis often begins before any rise in plasma oncotic pressure occurs, that it may be independent of any change in protein excretion, that it is accompanied by a drop in the output of aldosterone, that steroids can normalize early lesions in the epithelial layer of Bowman's membrane, and that abolition of proteinuria is paralleled by a rise in the concentration of serum protein and by a fall in the concentration of serum lipids. Lange[illegible] and Merrill[illegible] have been especially influential in establishing schedules which call for prolonged treatment with high doses, although differences of

pinion exist regarding the relative virtues of one agent over another. If ACTH is physiologically superior, it is also less convenient, for it cannot be taken by mouth. Patients—and therefore probably most physicians—prefer the steroids, which can be swallowed. Prednisone, prednisolone, methylprednisolone, and triamcinolone appear to be equally effective,[128] and all are superior to cortisone or hydrocortisone in that they are less apt to produce electrolyte disturbances, hyperglycemia, hypertension, convulsions, peptic ulceration, mental disturbances, and osteoporosis.

The schedule must be tailored to the patient's need, but the plan advised by Piel and Williams offers a satisfactory rule of thumb. It calls for either ACTH gel or prednisone in a daily dose of 1 mg. per pound of actual body weight until diuresis occurs and proteinuria has been suppressed for 1 week. At this point treatment is limited to 3 consecutive days of each week, and the dose is gradually reduced to a basal level of 20 mg. daily and held there until the urine has been protein free for about 1 year. This of course represents the ideal program, one to which perhaps 80 per cent of children and adults will respond, although it is rather easier to render patients edema free than it is to control the proteinuria.

What of the resistant patient? Induced hyperadrenocorticism is a severe metabolic dislocation, and the physician must ask himself whether slight amelioration of the renal lesion is worth the price. We have not used the high doses continuously for more than 6 weeks. Sometimes diuresis does not occur until the treatment is stopped, for reasons that may be related to temporary adrenal insufficiency. The majority of patients will lose a satisfactory amount of edematous fluid, but the few in whom proteinuria is unmodified require re-treatment after a short interval of rest—*provided* that the physician has done what he can to rule out such unresponsive diseases as lupus erythematosus, amyloidosis, or diabetes mellitus. Obviously, renal biopsy is of great value here. In Lange's hands[89] 88 per cent of 42 children and 68 per cent of 19 adults diuresed satisfactorily in the first course of treatment, and all but one of the resistant cases responded to re-treatment, one patient requiring five courses. Usually the dosage is increased in subsequent courses, and nitrogen mustard may be added to the steroid program. Mild azotemia and hypertension are not absolute contraindications. About 60 per cent of these cases were kept aproteinuric on intermittent steroid maintenance therapy. Merrill[90] also reported encouraging results from continuous treatment with ACTH gel. In so far as we know, hormonal therapy has not abolished proteinuria in patients who failed to diurese. Danowski, Mateer, and Puntereri[91] however, were able to abolish proteinuria in only 15 per cent of 54 miscellaneous cases of persistent proteinuria, but reported good results in about one third of the patients with glomerulonephritis and membranous glomerulosclerosis.

It may be useful to teach the patient on maintenance therapy to test his own urine for protein, either with 20 per cent sulfosalicylic acid or Clinitest papers. Proteinuria commonly increases during such stressful episodes as respiratory infections, sunburn, immunization procedures, severe physical exercise, etc., but very likely it is unnecessary to increase hormone dosage unless concomitant gain in weight occurs. A sliding scale may be worked out whereby the dosage is adjusted according to the degree of proteinuria, much as a diabetic patient adjusts his ration of insulin according to the degree of glucosuria. The relapse rate in the nephrotic syndrome is quite high unless treatment is meticulously adjusted to the patient's particular needs, and relapse may occur after years of clinical and laboratory control. Only when the patient has been virtually aproteinuric for about a year is it permissible to discontinue treatment, and this must be done by a very gradual reduction in hormone dosage over a period of 3 to 6 months.

Diet. Although Epstein mistakenly attributed the proteinuria to thyroid dysfunction, he was probably the first clinician to appreciate the relationship between pro

*[illegible] (2 to 4 Gm.) [illegible] (250,000 [illegible] Occasionally [illegible] gastric acid.

teinuria, hypoproteinemia, and edema,[a] and his advice concerning a high intake of protein is still heeded.[b] Diets very rich in protein are not well tolerated by children especially, and in any case no marked effect upon concentration of serum albumin need be expected, but even slight increase in retained nitrogen is useful. Anabolic steroids are theoretically useful from this standpoint also but have not been thoroughly evaluated yet in patients with serious renal disease. Carbohydrate is usually welcomed by the patient. Intake of salt and water ordinarily need not be much restricted. Fruit juices are rich in the potassium needed especially during steroid treatment. The important thing is a diet which maintains body weight and which is acceptable to the patient.

Physical activity. Prolonged bed rest is contraindicated. There is no reason why the patient should not do whatever he can do easily, although the renal vasoconstriction which normally occurs in the erect position and during exercise may be an argument in the minds of some for a nap after meals and for a long night's rest. The susceptibility of nephrotic patients to bacterial disease is probably an argument against hospitalization these days, although initial studies and treatment with ACTH may require it.

Statistics concerning the effect of treatment upon mortality have only temporary value. Evaluation is further complicated by failure of many authors to distinguish the varieties of glomerular disease which are associated with the nephrotic syndrome.[10] The recognition of disease of the basement membrane as an entity different from the proliferative endothelial response to streptococcal infections is a relatively recent achievement and makes it difficult to interpret even such important contributions as the classic study by Addis.

Whereas it is now generally conceded that the outlook for patients with poststreptococcal glomerulonephritis is quite good, only the dimmest outline of the natural history of the nephrotic syndrome is available. Perhaps the best account of what happens to patients when the nephrotic syndrome is unaccompanied by systemic disease in the pre-steroid era is a series from the Hospital of the Rockefeller Institute: about half of the children recovered spontaneously, but adults did so rarely. Among those who did so, the duration of the disease varied from 4 to 157 months, the mean duration being 2 to 4 years, depending upon the age group. Among those who died, the duration in the various age groups ranged from 29 to 82 months, but individual variations ranged from 2 to 192 months. This study suggested that urea clearance was a useful prognostic guide in individual cases: recovery was improbable unless the clearance returned to normal. The common causes of death were infection, heart failure, cerebral edema, and venous thrombosis. Rather surprisingly, the introduction of antibiotics had little effect upon survival rate.[11]

The impact of hormonal therapy is authoritatively discussed in each Annual Conference on the Nephrotic Syndrome published by the National Kidney Foundation. At the meeting in 1958, Riley[b] reported that 75 per cent of 554 children treated intensively were alive 4 years after the onset of the syndrome, whereas only 60 per cent of 318 control patients survived a similar length of time, and that a greater proportion of the living were in complete or partial remission. Goodman and Baxter obtained equally good results in adults and children: at least partial remissions occurred in three fourths of each group. Post and Eckel emphasized the fact that adults with the nephrotic syndrome have a much wider variety of degenerative renal lesions than do children and thought that less than 50 per cent of adults with the idiopathic variety respond satisfactorily. Nevertheless, they believed that all such patients should receive intensive therapy for at least 3 to 4 months and that prolonged maintenance therapy in those who do respond is necessary to prevent relapse. Not enough is known about the natural history of the disease, however, to justify dogmatic statements about possible effects of treatment upon long-term survival.

Summary

The nephrotic syndrome is apparently due to continued excretion (and destruction?) of serum albumin by the kidney. The chief clinical consequences are proteinuria, hypoalbuminemia, edema, lip

emia and susceptibility to infection and all too often to terminal renal failure

The nephrotic syndrome is associated with many renal diseases The most constant structural changes are seen by electron microscopy in the glomerular epithelium A reasonable facsimile of the disorder can be produced in animals by antikidney serum and by certain chemicals notably aminonucleoside The theory that it is due to the formation of autoantibodies is attractive but unproved

REFERENCES

1 Adams D A The pathophysiology of the nephrotic syndrome Arch Int Med 106 117 1960
2 Addis T Glomerular nephritis diagnosis and treatment New York 1948 The Macmillan Co
3 Albright F Bartter F C and Forbes A P The fate of human serum albumin administered intravenously to a patient with idiopathic hypoalbuminemia and hypoglobulinemia T A Am Physicians 62 204 1949
4 Allen A C The clinicopathologic meaning of the nephrotic syndrome Am J Med 18 277 1955
5 Armstrong S H J Mechanisms of action of serum albumin in internal medicine Am J Med 4 390 1948
6 Armstrong S H J Kark R M Schoenberger J A Shatkin J and Sights R Colloid osmotic pressures of serum proteins in nephrosis and cirrhosis relations to electrophoretic distributions and average molecular weights J Clin Invest 33 297 1954
7 Arnold J D Tarlov A R Spargo B and Brewer G J Subclinical diabetes mellitus in patients presenting with clinical chronic glomerulonephritis T A Am Physicians 71 186 1958
8 Barnett H L and Eder H A The nephrotic syndrome J Chron Dis 5 108 1957
9 Barnett H L Forman C W and Lawson H D The nephrotic syndrome in children Advances Pediat 5 53 1952
10 Baxter J H Goodman H C and Havel R J Serum lipid and lipoprotein alteration in nephrosis J Clin Invest 39 455 1960
11 Beattie J W Nephrotic syndrome following sodium bismuth tartrate therapy in rheumatoid arthritis Ann Rheumat Dis 12 144 1953
12 Bell E T A clinical and pathological study of subacute chronic glomerulonephritis including lipoid nephrosis Am J Path 14 691 1938
13 Bell E T Renal diseases ed 5 Philadelphia 1946 Lea & Febiger
14 Bergstrand A and Bucht H Electron microscopic investigations on glomerular lesions in diabetes mellitus (diabetic glomerulosclerosis) Lab Invest 6 29 1957
15 Berman L B and Schreiner G E Clinical and histologic spectrum of the nephrotic syndrome Am J Med 24 249 1958
16 Bjørneboe M Brun C Gormsen H Iversen P and Raaschou F The nephrotic syndrome I Histological changes illustrated by means of biopsy of the kidney Acta med scandinav (Suppl 266) 112 233 1952
17 Bjørneboe M Brun C Gormsen H Iversen P and Raaschou F The nephrotic syndrome II The effect of corticotrophin (ACTH) Acta med scandinav (Suppl 266) 112 249 1952
18 Blackman S S J On the pathogenesis of lipoid nephrosis and progressive glomerulonephritis Bull Johns Hopkins Hosp 57 70 1935
19 Blahd W H Fields M and Goldman L The turnover rate of serum albumin in the nephrotic syndrome as determined by I[131] labeled albumin J Lab & Clin Med 46 747 1955
20 Blaine J D Hardwicke J and Whitfield A G W The nephrotic syndrome associated with thrombosis of the renal veins Lancet 2 1209 1954
21 Bloom W L and Seegal D The nephrotic phase its frequency of occurrence and its differential diagnostic value in determining the nature of the renal lesion 120 patients who died of renal failure Ann Int Med 25 15 1946
22 Borst J G The maintenance of an adequate cardiac output by the regulation of the urinary excretion of water and sodium chloride an essential factor in the genesis of edema Acta med scandinav (Suppl 207) 130 1 1948
23 Bradley S E Bradley G P Tyson C J Curry J J and Blake W D Renal function in renal diseases Am J Med 9 766 1950
24 Bradley S E and Tyson C J The nephrotic syndrome New England J Med 238 223 1948
25 Broch O J and Brodwall E Urinary proteins in renal diseases Acta med scandinav 160 355 1958
26 Cartwright G E Bibler C J and Wintrobe M M Studies on copper metabolism XI Copper and iron metabolism in the nephrotic syndrome J Clin Invest 33 685 1954
27 Cavelti P A Pathogenesis of glomerulonephritis and rheumatic fever Arch Path 44 119 1947
28 Chinard F P Lauson H D Eder H A Greif R L and Hiller A A study of the mechanism of proteinuria in patients with the nephrotic syndrome J Clin Invest 33 621 1954
29 Chinard F P Lauson H D Eder H A and Greif R L Plasma volume changes following the administration of albumin to patients with the nephrotic syndrome J Clin Invest 33 629 1954
30 Cruickshank B and Hill A G S The histochemical identification of a connective tissue type in the rat J Path & Bact 66 283 1953

31 Danowski T S Mateer F M nd Punteren A J ACTH of adrenocortical steroid therapy of proteinuria in adolescents and in adult Am J M Sc 237:545 1959
32 Mateer F M Wiegand F A Greenm L Weber C J Kunkel G A and Danowski T S Corticotropin (ACTH) therapy of nephrotic syndrome in children A M A J Dis Chil 93 591 1957
33 Dingman J F and Yoffee H F Effect of cal um gluconate and adrenal sterol on sodium and w ter excretion in patients w th cirrhos and ascites New England J Med 262 585 1960
34 Earle D P J Gl merulonephritis Disease Month January 1956
35 Ehrich W E Glomerular nephritis nd lipid nephros with identities and mechani ms J Chron Dis 5 14 19 7
36 Eisen H M Sherman B nd Pres man D The zone of localization of antibodies IX The properties of anti rat lung serum J Immunol 65 543 19 0
37 Elasch H Sellers A L Rosenfeld S and Marmoston J Protein metabolism in the mammalian kidney J Exper Med 101 129 1955
38 Ellis A N tural hi tory of Bright disease Lancet 1 1 1942
39 Epstein A A The nature and treatment of chronic parenchymatou nephritis (nephrosis) J A M A 69 444 1917
40 Farquhar M G Vernier R L and Good R A An electron microscopic study of the glomerulus in nephrosi glomerulonephritis nd lupus erythematosus J Exper Med 106 649 1957
41 Farquhar M G Vernier R L nd Good R A Studies of familial nephrosis II Glomerular changes observed th electron micro scope Am J Path 33 91 19 7
42 Farrell G Steroidogenic properties of ex tracts of beef diencephalon Endocrinology 65 29 1959
43 F hlberg A M Hypertension and nephritis ed 65 Philadelphia 1954 Lea & Febiger p 445
44 Folli G Pollak V E Reid R T W Pirani C I and Kark R M Electron m croscopic tudies of rever ible glomerular lesions in the adult nephrotic syndrome Ann I t Med 49 775 1958
45 Folli G Pollack V F Reid R T W P ran C L and Kark R M Electron microscopic studies of renal biopsies taken from nephrot patients before and after diuresis J Lab & Clin Med 50 813 (Abst) 1957
46 Folli G Pollack V F Reid R T W Pi rani C L and Kark R M Electron microscop studies of reversible glomerula lesions in the adult nephrotic syndrome Ann I t Med 49 775 1958
47 Ford P A I im tations and pote tial and actual side eff cts of thiazide deri tives *I* Mover J H nd Fuchs M Edema—mecha ms and management Philadelphia 1960 W B Sa nders Co pp 289 29
48 Fouts P J Corcoran A C and Page I H Observations on the clinical nd f nctional course of nephrotoxic nephrosis in dogs Am J M Sc 201:313 1941
49 Frenk S Antonowicz I Craig J M and Metcoff J Experimental nephrotic syndrome induced in rats by aminonucleoside Renal lesions and body electrolyte composition Proc Soc Exper Biol & Med 89 424 1955
50 Freedman L R Inapparent diabetes mel litus as cause of renal insufficiency due to Kimmelstiel Wilson lesions B ll Johns Hopkins Hosp 100 132 19 7
51 Freedma P Peters J H and Kark R M Localization of gamma-globulin in the diseased kidney Arch I t Med 105:524 1960
52 Freeman T and Joekes A M Nephrotic proteinuria a t bular lesion? Acta med scandina 1 43 1957
53 Freeman T and Mathew C M Analysis of the behavior of I[131] albumin in the normal subject and nephrotic patient Strahlentherap Sonderbd 38 283 1958
54 Geer J C Strong J P McGill H C Jr nd Muslow I Electron microscopic obser tions on the localization of myloid in the kidney in secondary amyloidosis Lab Invest 1554 1958
55 Gellman D D Pirani C L Soothill J F Muehrcke R C and Kark R M Diabetic nephropathy linical pathologic study based on renal biopsies Medicine 38:321 1956
56 Gellman D D Pirani C L Soothill J F Muehrcke R C Maduros W and Kark R M Structure and function in diabetic nephropathy The importance of diffuse glomerulosclerosis Diabetes 8 51 1959
57 Gilbertson A S and Bashour F Use of malaria therapy in the nephrotic syndrome J A M A 160 25 30 1956
58 Giles H M Pugh R C B Darmady E M Stranack F and Woolf L I The nephrotic syndrome in early infancy a report of three cases Arch Dis Childhood 32 167 19 7
59 Gitlin D nd Cornwell D Pla ma lipo protein metabolism in normal indiv duals and in children with nephrotic syndrome (Ab stract) J Clin Invest 35 06 1956
60 Gitlin D Janeway C A and Farr I E Studies on the metabolism of plasma proteins in the nephrotic syndrome I Albumin globu lin nd iron binding globulin J Clin Invest 35 44 1956
61 Gitlin D Corn ell D G Nakasato D Oncley J L Hughes W L J and Janeway C A Studies on the metabolism of plasma proteins in the nephrotic syndrome II The lipoproteins J Clin Invest 37 172 1958
62 Goodman H C and Baxter J H The nephrotic syndrome Clinical obser tions on therapy with prednisone and other steroids J A M A 16 1 98 19 7
63 Goodman M Greenspon S A and Krakower C A The antigenic composition of the various anatomic structures of the canine kidney J Immunol 96 1955

64. Gregoire, F., Malmendier, C., and Lambert, P. P.: The mechanism of proteinuria and a study of the effects of hormonal therapy in the nephrotic syndrome, Am. J. Med. 25:516, 1958.
65. Harm, W. S.: Unpublished observations.
66. Harkin, J. C., and Recant, L.: The earliest lesion in aminonucleoside nephrosis: an electron microscopic study (abstract), Am. J. Path. 34:559, 1958.
67. Harrison, C. V., Milne, M. D., and Steiner, R. E.: Clinical aspects of renal vein thrombosis, Quart. J. Med. 25:285, 1956.
68. Hartroft, M. E.: Some metabolic and structural characteristics of experimental nephrosis (editorial), Am. Heart J. 58:483, 1959.
69. Heidor, G. H.: The effect of corticotrophin (ACTH) on ammonia production in the nephrotic syndrome, Am. J. M. Sc. 231:644, 1956.
70. Heymann, W., and Lund, H. Z.: Nephrotic syndrome in children, Pediatrics 7:691, 1951.
71. Heymann, W., Gilkey, C., and Lewis, M.: The prognostic significance of globulinuria in the nephrotic syndrome: electrophoretic studies of urinary proteins in the nephrotic syndrome and acute glomerulonephritis, A.M.A. J. Dis. Child. 91:510, 1956.
72. Heymann, W., Hackel, D. B., Harwood, S., Wilson, S. G. F., and Hunter, J. L. P.: Production of nephrotic syndrome in rats by Freund's adjuvants and rat kidney suspension, Proc. Soc. Exper. Biol. & Med. 100:660, 1959.
73. Heymann, W., Nash, G., Gilkey, C., and Lewis, M.: Studies on the causal role of hypoalbuminemia in experimental nephrotic hyperlipemia, J. Clin. Invest. 37:808, 1958.
74. Hooft, C., and Herpol, J.: Aminoaciduria in the course of lipoid nephrosis in children. The influence of ACTH, Acta paediat. 48:135, 1959.
75. James, J., Gordillo, G., and Metcoff, J.: Effects of infusion of hyperoncotic dextran in children with the nephrotic syndrome, J. Clin. Invest. 33:1346, 1954.
76. Janeway, C. A.: Diuresis in children with nephrosis: comparison of response to injection of normal human serum albumin and to infection, particularly measles, Tr. A. Am. Physicians 61:108, 1948.
77. Joekes, A. M., Heptinstall, R. H., and Porter, K. A.: The nephrotic syndrome. A study of renal biopsies in 70 adult patients, Quart. J. Med. 27:495, 1958.
78. Kaitz, A. L.: Albumin metabolism in nephrotic adults, J. Lab. & Clin. Med. 53:186, 1959.
79. Kark, R. M., Pirani, C. L., Pollack, V. E., Muehrcke, R. C., and Blainey, J. D.: The nephrotic syndrome in adults: a common disorder with many causes, Ann. Int. Med. 49:751, 1958.
80. Kark, R. M., Pirani, C. L., Pollack, V. E., Muehrcke, R. C., and Blainey, J. D.: The nephrotic syndrome in adults: a common disorder with many causes, Ann. Int. Med. 49:751, 1958.
81. Kay, C. F.: The mechanism of a form of glomerulonephritis. Nephrotoxic nephritis in rabbits, Am. J. M. Sc. 204:483, 1942.
82. Keitel, H. G., Goodman, H. C., Havel, R. J., Gordon, R. S., and Baxter, J. H.: Nephrotic syndrome in congenital quartan malaria, J.A.M.A. 161:520, 1956.
83. Kemp, J. A., and Findley, T.: The choice of a diuretic with special reference to hydrochlorothiazide, J. M. A. Georgia 48:389, 1959.
84. Kimmelstiel, P., and Wilson, C.: Intercapillary lesion in the glomeruli of the kidney, Am. J. Path. 12:83, 1936.
85. Kimmelstiel, P.: Glomerulosclerosis, J. Mt. Sinai Hosp. 23:657, 1956.
86. Krakower, C. A., and Greenspon, S. A.: Localization of the nephrotoxic antigen within the isolated renal glomerulus, A.M.A. Arch. Path. 51:629, 1951.
87. Krupp, M. A.: Urinary sediment in visceral angiitis (periarteritis nodosa, lupus erythematosus, Libman-Sacks disease): quantitative studies, Arch. Int. Med. 71:54, 1943.
88. Kunkel, H. G., and Slater, R. J.: Lipoprotein patterns of serum obtained by zone electrophoresis, J. Clin. Invest. 31:677, 1952.
89. Lange, K., Strang, R., Slobody, L. B., and Wenk, E. J.: The treatment of the nephrotic syndrome with steroids in children and adults, Arch. Int. Med. 99:760, 1957.
90. Lange, K., Wasserman, E., and Slobody, L. B.: Prolonged intermittent steroid therapy for nephrosis in children and adults, J.A.M.A. 168:377, 1958.
91. Letter, L.: The capillary vascular lesion in diabetes mellitus. Its clinical manifestations and significance, Diabetes 4:280, 1955.
92. Longcope, W. T.: Some observations on the course and outcome of hemorrhagic nephritis, Internat. Clinics (new series) 1:1, 1938.
93. Luetscher, J. A., Jr., Hall, A. D., and Kremer, V. L.: Treatment of nephrosis with concentrated human albumin. I. Effects on the proteins of body fluids, J. Clin. Invest. 28:700, 1949.
94. Luetscher, J. A., Jr., Hall, A. D., and Kremer, V. L.: Treatment of nephrosis with concentrated human serum albumin. II. Effects on renal function and on excretion of water and some electrolytes, J. Clin. Invest. 29:896, 1950.
95. Luetscher, J. A., Jr., and Mulrow, P. J.: The nephrotic syndrome, Disease-a-Month, August 1956.
96. Martin, N. H.: Primary protein deficiencies with special reference to the specific plasma proteinemia, Lect. Sci. Basis Med. 5:165, 1955-56.
97. Masugi, M.: Über die experimentelle Glomerulonephritis durch das spezifische antinieren Serum, Beitr. path. Anat. 92:429, 1933.
98. Mellors, R. C., and Ortega, L. G.: New observations on the pathogenesis of glomerulonephritis, lipoid nephrosis, periarteritis nodosa and secondary amyloidosis in man, Am. J. Path. 32:455, 1956.
99. Merrill, A. J.: Use of steroids in renal disease, Tr. Am. Clin. & Climatol. A. 68:193, 1956.

100 Merrill A J Whan J and Timberlake L F Continuous therapy of nephrotic syn drome in children with corticotrophin gel Arch Int Med 94 925 1954

101 Metcoff J James J A Gordillo G and Antonowicz I Renal electrolyte transport in normal and nephrotic children Effects of simultaneous infusion of carbonic anhydrase inhibitor and norepinephrine hormone J Lab & Clin Med 46 333 1955

102 Metcoff J Kelsey W M and Janeway C A The nephrotic syndrome in children An interpretation of its clinical biochemical and renal hemodynamic features variations of a single type of nephron disease J Clin Invest 30 471 1951

103 Metcoff J Nakasone N and Rance C P On the role of the kidney during nephrotic edema potassium excretion and sodium retention J Clin Invest 33 665 1954

104 Milne M D Diseases of the kidney and genitourinary tract *I* Thompson R H S and Kinr F J Biochemical disorders in human disease New York 1957 Academic Press pp 117 241

105 Movat H Z The fine structure of the glomerulus in amyloidosis A M A Arch Path 69 32 1960

106 Movat H Z and McGregor D D The fine structure of the glomerulus in membranous glomerulonephritis (lipoid nephrosis) in adults Am J Clin Path 32 109 1959

107 Muehrcke R C Kark R M Pirani C L and Pollack V E Lupus nephritis clinical and pathological study based on renal biopsies Medicine 36 1 1957

108 Muehrcke R C Pirani C L Pollack V E and Kark R M Primary renal amyloidosis with the nephrotic syndrome studied by serial biopsies of the kidney Guy Hosp Rep 104 295 1955

109 Muehrcke R F The fingernails in chronic hypoalbuminemia new clinical sign Brit M J 1 1327 1956

110 Munk F Klinische Diagnostik der degenerativen Nierenerkrankungen I Sekundar-degenerative primaer-degenerative Nierenerkrankungen II Degenerative Syphilisniere Ztschr klin Med 78 1 1913

111 Munk O and Nasseu N I Development of nephrotic syndrome during treatment with mercurial diuretics Acta med scandinav 153 307 1956

112 Murphy F D and Schulz E G Natural history of glomerulonephritis Arch Int Med 98 783 1956

113 Nisonoff A and Pressman D Mechanism of antibody antigen reaction Science 122 1272 1955

114 Phillips I Calvin J K and Kagan B M Nephrotic syndrome in children observations on clinical course and influence of sulphonamide and antibiotic therapy A M A J Dis Child 85 451 1953

115 Pd C F Dong L Modern M O Goodman J R and Moore R The glomerulus in experimental renal disease in rats as observed by light and electron microscopy J Exper Med 102 573 1955

116 Piel C F and Williams G F Long-continued drug hormone therapy in childhood nephrosis J Am M Women s A 12 273 1957

117 Platt R Stewart A F and Emery E W The aetiology incidence and heredity of pre-eclamptic toxemia of pregnancy Lancet 1 552 1958

118 Pollack V F Kark R M Pirani C L Shafter H A and Muehrcke R C Renal vein thrombosis and the nephrotic syndrome Am J Med 21 496 1956

119 Pollack V F Pirani C L Kark R M Muehrcke R C Freda V C and Nettles J B Reversible glomerular lesions in toxemia of pregnancy Lancet 2 59 1956

120 Pollack V E Pirani C L Muehrcke R C Pulos I C Kark R M and Steck I F On renal involvement in systemic lupus erythematosus and other so-called collagen diseases Arthritis Rheum 1 704 1958

121 Post R S and Eckel R E Hormone therapy of the adult nephrotic syndrome of unknown etiology J Chron Dis 12 211 1960

122 Proceedings of the Sixth Annual Conference on the Nephrotic Syndrome (J Metcoff editor) National Nephrosis Foundation Inc 1955 p 189

123 Proceedings of the Eighth Annual Conference on the Nephrotic Syndrome (J Metcoff editor) National Nephrosis Foundation Inc 1957 p 22

124 Proceedings of the Ninth Annual Conference on the Nephrotic Syndrome (J Metcoff editor) National Nephrosis Foundation Inc 1958
 Gitlin Baxter Rodbell Gordon Bailey pp 82 14
 b Lange et al pp 13 39
 Goodman et al pp 61 81

125 Proceedings of the Tenth Annual Conference on the Nephrotic Syndrome (J Metcoff editor) The National Kidney Disease Foundation 1959
 Kark p 215
 b Lange p 11
 Heymann p 17
 d Arneil p 249
 Kramer p 66
 f Fliss p 87
 g Heymann p 172
 h Lange p 37
 Lange p 244
 j Lange p 278
 k Riley p 273
 l Farquhar p 2

126 Protein losing gastroenteropathy (editorial) Lancet 1 351 1959

127 Rand I S Plasma expanders J A M A 150 10 1952

128 Recant L Abnormality in thyroxine binding in nephrosis (abstract) J Clin Invest 35 730 1956

129 Recant L Borowsky B and Dubach U Aminonucleoside glomerulonephritis in rats Proceedings of the 31st Annual Session of the

America College of Physicians 1960 p 113
130 Reed R W and Mathieson B H Experimental nephritis due to type specific streptococci I The effect of a single exposure to type 12 streptococci J Infect Dis 95 191 1954
131 Reid R T W Electron microscopy of glomeruli in nephrotoxic serum nephritis Australian J Exper Biol & M Sc 34 143 1956
132 Robbins J Rall J E and Petermann M L Thyroxine binding by serum and urine proteins in nephrosis qualitative aspects J Clin Invest 36 1333 1957
133 Rosenman R H Friedman M and Byers S O The causal role of plasma albumin deficiency in experimental nephrotic hyperlipemia and hypercholesterolemia J Clin Invest 3 5 ? 1956
134 Roscoe M H The nephrotic syndrome Quart J Med 25 353 1957
135 Rose D S The similarity of the protein mixtures derived from serum by selective ultrafiltration to the urine proteins in the nephrotic syndrome J Physiol 135 1 2P 1956
136 Rytand D A Onset of the nephrotic syndrome during reaction to bee sting Stanford M Bull 13 24 1955
137 Rytand D A Fatal anuria nephrotic syndrome and glomerular nephritis as sequel of dermatitis of poison oak Am J Med 5 549 1948
138 Rytand D and Cox A J J Polycyclic nephrotic syndrome Am J Med 22 297 19
139 Schreiner G E 3 D for diagnosis G P 9 70 1954
140 Schreiner G E Some observations on telescoped urinary sediments Ann Int Med 42 836 1955
141 Schreiner G E and Berman L B Experience with 150 consecutive renal biopsies South M J 50 733 195
142 Schwartz M and Thomsen B Idiopathic or hypercatabolic hypoproteinemia—case examined by I[131] labeled albumin Brit M J 1 14 1957
143 Seegal B C and Bevan M The production of glomerulonephritis by immunologic method J Chron Dis 153 1957
144 Seller A L Unpublished observations Quoted by Adams D A The pathophysiology of the nephrotic syndrome A M A Arch Int Med 106 117 1960
145 Shreeve W W Hutchin M E Harper H A Miller C D and Doolan P D Excretion of amino acids in nephrosis Proc Soc Exper Biol & Med 88 510 1955
146 Spargo B McCartney C P and Winemiller R Glomerular capillary endotheliosis in toxemia of pregnancy Arch Path 68 593 1959
147 Spiro D The structural basis of proteinuria in man Electron microscopic studies of renal biopsy specimens from patients with lipid nephrosis amyloidosis subacute and chronic glomerulonephritis Am J Path 35 47 1959
148 Steiger W A Zarafonetis C J D Miller G M Seifter J and Baeder D H Preliminary report on the effects of a plasma lipid mobilizing factor in man Am J M Sc 232 605 1956
149 Sterling K The turnover rate of serum albumin in man as measured by I[131] tagged albumin J Clin Invest 30 1228 1951
150 Squire J B The nephrotic syndrome Advances Int Med 201 1955
151 Squire J R Blainey J D and Hardwicke J The nephrotic syndrome Brit M Bull 13 43 1957
152 Taylor P D Corcoran A C and Page I H Treatment of the nephrotic syndrome with nitrogen mustard J Lab & Clin Med 36 996 1950
153 Ulstrom R A Smith N J and Meumlich E M Transient dysproteinemia in infants a new syndrome A M A J Dis Child 92:219 1956
154 Vernier R L Brunson J and Good R A Studies on familial nephrosis I Clinical and pathologic study of four cases in a single family A M A J Dis Child 93 469 1957
155 Wachstein M and Lange K Proteinuria and tubular atrophy in the rat Their relationship as studied by enzymatic histochemistry with special reference to the antirabbit kidney serum nephritis and aminonucleoside nephrosis Lab Invest 9 371 1960
156 Wilson V K Thomson M L and Holzel A Mercury nephrosis in young children with special reference to teething powders containing mercury Brit M J 1 358 1952
157 Woolf L I and Giles H McC Urinary excretion of amino-acid and sugar in the nephrotic syndrome A chromatographic study Acta paediat 45 489 1956
158 Worthen H G Vernier R L and Good R A The syndrome of infantile nephrosis (abstract) A M A J Dis Child 96 585 1958
159 Wren J C and Nutt R L Nephrotic syndrome occurring during paramethadione therapy J A M A 153 918 1953

Annotations

The preservation of myocardial function during open heart surgery

In the final analy is the succes or failure of intracardiac operation w ll largely depend on the adequacy of the reconstructiv procedure the extent of secondary changes in other organs uch as the pulmonary ascular bed nd the degree to which the contractile force nd energy reserves of the myocardium has been conserved When severe pulmonary hypertension congestiv heart failure or advanced myocardial hypertrophy are present the last group of factors ume critical importance because the relationship bet een myocardial reserves and the obligatory work load demanded of the heart in the postoperativ period may be in fine state of balanc

The clinical doption of many features of current surgical practice has preceded proper ev luation of their effects on m ocardial function Total bod perfusion even when prolonged for 2 hours has no detectable effect on entricular function Inci ion of the entricle on the other hand invariably results in immediate impairment of function the degree of impairment being related t the length and ts of the inci on The late effects of en triculotomy are irtually unknow and constitute an important field for further study

Hypothermia is frequently induced during total body perfusion From the evidence ailable[4] it would ppear that moderate hypothermia ha no immediate effect on entricular function but clearly deep hypothermia has[4] the heart frequently fails the temperature is reduced below 25 C It presumed but quite unproved that these effects are completely re ersed on rewarming The histologic changes which follow hypothermia demon strated by Sarajas Senning and Kaplan probably hav functional accompaniments

The deliberate induct on of asystol by the Melrose technique has been show by number of workers[4] to result in lasting impairmen of function and should probably be discarded as being more harmf l tha simple anoxic arrest Hypothermia appears to lessen the damage done by the use both of potassium citrate[4] and of prolonged anoxic arrest The consensus of opinion that whereas simple anoxic arrest is better tolerated than potassium induced asystole anoxic arrest for 20 minutes results in gnificant reduction in entricular function Interrupted aortic occlusion llowing coronary circulation briefly after each 5 minutes of card ac anox ppear to conserv entricular function better than an of the other techniques which ha been ad ocated Some further latitude may be prov ded for the surgeon if interrupted ort oc l mbi ed w th moder t h pothermia

Whatever the technique of nducing asystole the paramount importance of oiding passiv di tention of either the right or left ide of the heart by adequate decompression now ell recognized It similarly pparent to those working in the field that the heart takes t least few minutes to recover even partially from an in ult be t anoxic or chemical It is advisable therefore to ontinue total bypa for t least 5 minutes after the release of the aortic lamp and to submit the heart gradually t ts full work load after further period of partial bypas

E en the anesthetic agents we use hav signific t effects on entricular f nction but these are prob ably completely re er ible Halothane which has much commend t as an anesthetic agent in cardiac surgery has quit marked depressant effect on ardiac contractility in the concentrations which are used in cl nical practice[10] Further study of other agent is necessary

It is clearly impo ible in short review to gain an dequate per pectiv of the arious factors which ha been mentioned It probable that these effects are add tiv nd summate maximally in the period immediately after bypass Although some are learly reversible our knowledge of the late effects of entriculotomy deep h pothermia and induced asystole quit fragmentary and w ts further elucidation

Surgery is both art and science and judgment is often the final arbiter A sound knowledge of the functional effects of the techniques we hould help u to make the best compromise in each case between the often onflicting interests involved in on the one hand conserving the function of the myocardium and on the other providing ideal conditions for urgical repair

The compromise reached will necessarily ary from case to case I oper tion on patients in the older age group or on patients who ha been in failure or who ha gross entricular hypertrophy it ca be presumed that the myocardial reserves are low nd surgical technique should be designed around the concept of maximally conserving these reserves I some younger pat ents w thout these

ac ompaniments t is perhaps justifiable to take akulated ri k in order to provide better access so that complete repair of the defect is ensured There can be no substitute in these matters for mature surgical judgment based on an adequately studied pa t experience

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REFERENCES

1 Sterling G R Stanley P H and Lillehei C W The effects of cardiac bypa s and entric lotomy upon right entricular f nction w th report of successful closure of ventricular eptal defect by antriotomy S Forum 8 433 1958
2 McMillan I K R Case R B Stainsby W W and Welch G H The hypothermic heart work potential and coronary flow Thora 12 208 1957
3 Drew C E Keen G nd Benazon D B Profound hypothermia Lancet 1 745 1959
4 Sarajas H S S Senning A and Kaplan J Heart damage in dogs ubjected t hypother mia circulatory arrest and cardiac urgery Am Heart J 52 536 1956
5 Braunwald N S Waldhausen J A and Cornell W P Left ventricular function following elective cardiac arrest Circulation 20 676 1959
6 Wernich W L Jones R W and Burke M F The effect of elective cardiac arrest induced by potassium citrate and acetylcholine on ventricular function S Forum 10 528 1960
7 Sterling G R Morris K N and Race D The effect of induced asystole on ventricular function Australia & New Zealand J Surg 1960 (In press)
8 Cooper T William V L Zafiracopoulos I and Hanlon C R Myocardial function after electiv cardiac arrest during hypothermia Surg Gynaec & Obst 109 423 1959
9 Shumway N E Lower R R and Stofer R C Selective hypothermia of the heart in anoxic cardiac arrest Surg Gynec & Obst 109 750 1959
10 Sterling G R Morris K N Orton R H Books W C Race D Kinross F Thompson J W and Crosby W Halothane and circula tory occlusion some experimental and clinical observations Brit J Anaesth 32 262 1960

Ultrasonic cardiography

The method inaugurated by Edler and Hertz in 1954 at the University of Lund Sweden has been introduced t the I Medical Department in Duesseldorf[3,4] and t some other medical linics in Germany[5,6] as routine procedure in order to estimate the degree of mitral steno is The physical principle is generally know the registration of ultrasonic echo which originates from borderlines of different media If sonic energy is sent through the human heart a partial sonic reflection—in this case an ultrasonic echo—will arrive t the border between cardiac walls and the surrounding tissue that is between the cardiac walls and the blood

For the generation of ultr onic energy and the sim ltaneous receiving of the reflected sonic energy piezoelectric electroacoustic transducer is used (sound frequency 1 2 5 megacycles) The sound radiation is not a continuous but a periodic one (the duration of impulse is 1 to 7 µsec.) The re flected sound impulse is reconducted to the piezo-electric quartz which in the meantime has been sw tched onto reception For visualization a cathode-ray oscillograph is used after amplification The instrument used is commercially available ultra sonic impul e set which has been developed for the testing of material

If the reflecting cardiac wall is moved toward the ultrasonic tran mitter the echos on the fluorescent screen will move toward the X axis This movement is a time function curve Through the use of a transm tting frequency of 200 impulses per second t is possible to register the movement of special cardiac walls with an accuracy of me surements of 5 microseconds

If in the human subject the ultrasonic transmitter is placed over the third intercostal area on the left parasternal side a moving curve is recorded which shows the characteristic forms of a enous curv with two maxima t the time of tral systole and having t the refilling phase a minimum t the time of ventricular systole In ca e of incomplete or complete trioventricular block the first maximum consta tly appears 0 07 second after the beginning of the P wa in the ECG This maximum is absent in case of tral fibrillation In case of atrial flutter mechanical flutter waves may be registered

In mitral stenosis the second maximum is recorded synchronously w th the mitral opening snap in the phonocardiogram The following part of the curve which corresponds to the time of entricu lar filling that is the atrial depletion after the opening of the mitral valve progresses the planer the greater the degree of mitral stenosis In other words the registered part of the heart will move more slowly from the che t wall the greater the degree of mitral stenosis The closeness of the quantitative correlations to the anatomic condition which is in accordance with the opening area of

the mitral valve has been investigated in the mean time on more than 1 500 patients with mitral valvular disease

It is still unknown at which part of the cardiac wall the sound reflection takes place By the direction of the sound beam and the special topography by the form of the curve in respect to the influence of arrhythmia or the synchronous registration of atrial pressure curves or the characteristic forms of the curve in case of mitral stenosis one can presume that the movement of the anterior wall of the left atrium is registered The recent investigations of Edler[1] on dead hearts suggest that the movements of the mitral valve itself are recorded

Since the ultrasonic waves can penetrate the cardiac wall—in contrast to kymography—tumors of the left atrium which may imitate mitral stenosis and large thrombus will give typical ultrasonic echo curves In the case of hydropericardium the movement of the anterior wall of the left ventricle can be recorded and from the distance of the sound generator to the anterior cardiac wall the amount of effusion can be estimated If the sound generator is applied over the second intercostal area on the left parasternal side the moving curve of the A pulmonalis can be registered

If the third intercostal area is chosen using medial and dorsal direction of the sound beam the movement of the aortic valve in the human heart in situ can be recorded (Edler 1960) Probably by this means the distinction between valvular and subvalvular aortic stenosis is possible But in contrast to mitral valvular disease in this case there are still some technical difficulties of recording Practical application to diagnostic procedure in the case of aortic valvular disease cannot yet be considered

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REFERENCES

1 Edler J and Hertz C H Kungl Fysiogr Sällskapets in Lund forhandlingar 24 No 5 1954
2 Edler J and Gustafson A Acta med scandinav 159 154 1957
3 Edler J Gustafson A Karlefors T and Christensson B III Europäischer Kardiologenkongress Rome 1960
4 Effert S Erkens H and Grosse Brockhoff F German M Month 2 325 1957
5 Effert S Arch Kreislaufforsch 30 13 1959
6 Effert S and Domanig F German M Month 4 1 1959
7 Effert S Hertz C H and Böhme W Ztschr Kreislaufforsch 48 230 1959
8 Gassler E and Samlert H Ztschr Kreislaufforsch 47 291 1958
9 Schmitt W and Braun H Ztschr Kreislaufforsch 49 214 1960

The electrocardiogram in pulmonary emphysema and chronic cor pulmonale

The electrocardiographic changes which occur in pulmonary emphysema and in chronic cor pulmonale have been well described Although some definitions of chronic cor pulmonale include a wide variety of conditions with right heart failure secondary to pulmonary hypertension we shall use the term chronic cor pulmonale in its restricted sense of that of right heart disease secondary to pulmonary emphysema

The electrocardiographic patterns which have been described in pulmonary emphysema and chronic cor pulmonale include the following (1) ÂP (frontal mean P wave axis) > +60 to +90 resulting in tall peaked P waves in Leads II III and V often accompanied by prominent T waves (2) ÂQRS (frontal mean QRS axis) +90 or greater (right axis deviation vertical heart) (3) transition zone displaced to the left (clockwise rotation) with RS pattern in left precordial leads (4) negative or predominantly negative QRS complexes (rS QS) in all precordial leads (5) low voltage QRS in limb and/or left precordial leads (6) S_1 Q_3 pattern (7) S_1 S_2 S_3 syndrome (8) T wave inversion in right precordial leads (9) abnormal left axis deviation (10) classic right ventricular hypertrophy (RVH) in Lead V (V$_{3R}$) with dominant R waves (Rs R qR QR qRs) (11) rSR in Lead V (V$_{3R}$) (12) complete right bundle branch block (13) normal or nonspecific tracing

The distinction between the electrocardiographic changes that may be produced by emphysema alone and those that are due to associated right ventricular hypertrophy is at times difficult To attempt to make such a distinction however is important since changes in the electrocardiogram may be occasionally the earliest objective manifestation of cor pulmonale Conversely the effect of pulmonary emphysema alone on the electrocardiogram should not be misdiagnosed as that of right ventricular hypertrophy It will be best to consider the effect of each of these factors separately

Milder degrees of pulmonary emphysema may have no recognizable effect on the electrocardiogram More severe degrees of emphysema (as measured by pulmonary function tests) however may bring about certain characteristic changes in the electrocardiogram ?

The heart becomes vertically placed because of the low diaphragmatic position. This results in vertical electrical position of the heart and a rightward deviation of the mean QRS and P waves in the frontal plane. Because of the low lying position of the heart the customary precordial lead positions will be high and most or all of the exploring leads may be in the area of relative negativity for the mean QRS vector and record predominantly negative QRS deflection from Leads V1-V6 (rS or QS). If the heart is not displaced quite so low in the chest the null plane of the mean QRS vector may be relatively parallel to the precordial leads and these will display transitional type of complex (RS) even as far to the left as Lead V6. Posterior rotation of the mean QRS vector in the horizontal plane also contributes to the shift of the transition zone to the left (marked clockwise rotation). When the heart assumes a vertical position there tends to be clockwise rotation on the longitudinal axis of the QRS electrical field (not to be confused with anatomic rotation of the heart, for which there is little evidence[1]) with the appearance of an S1 and Q3. The QRS voltage is low because (1) the electrodes are relatively far removed from the ventricles, (2) the emphysematous lung is a poor electrical conductor, (3) the spatial QRS vector tends to be posteriorly directed with the resultant small projection on the frontal plane.

It thus readily becomes apparent that emphysema alone may produce virtually all of the electrocardiographic patterns that have been enumerated except perhaps the more classic ones of RVH in the right precordial leads, the more marked degrees of right axis deviation (> + 110°), and right ventricular conduction defect. The issue is further complicated by the fact that even advanced cor pulmonale with considerable anatomic RVH only rather uncommonly results in high voltage in the right precordial leads and in fact may exhibit no electrocardiographic evidence of RVH. Right ventricular conduction defects are suggestive but rarely aid diagnosis of right ventricular enlargement in cases of pulmonary emphysema.

The classic P pulmonale pattern may occur with emphysema alone or may be the sole electrocardiographic manifestation of anatomically proved cor pulmonale. Some authors believe that these P wave changes are not caused by vertical position alone but may result from right atrial enlargement (dilatation and/or hypertrophy).

The abnormal left axis deviation (in the range of −90°) occasionally encountered in severe pulmonary emphysema has been ascribed to abnormal transmission of electrical potential or to associated left ventricular enlargement or conduction disturbance, or in fact is actually marked right axis deviation. Another proposed explanation is the so-called pseudo[illegible] phenomenon,[11] in which the posteriorly directed mean QRS force nearly perpendicular to the frontal plane and only slightly superior shift in this vector in the sagittal plane will project it on the frontal plane as a markedly superiorly directed force.

Abnormal QRS patterns (qR, QS) suggestive of anteroseptal, anterior, and anterolateral myocardial infarction have been well documented in cases of chronic cor pulmonale. This has been attributed to right ventricular dilatation with or without RVH as well as to the posterior orientation of the mean QRS vector. Abnormal Q waves in Leads II, III, and aVF simulating inferior myocardial infarction have also been described occasionally in chronic cor pulmonale.

Arrhythmias other than sinus tachycardia are uncommon in chronic cor pulmonale but may occur.

It has been demonstrated in patients with chronic cor pulmonale that if the electrocardiographic pattern of RVH is present the mean pulmonary arterial pressure will exceed 30 mm. Hg, and those patients with chronic cor pulmonale whose total pulmonary vascular resistance exceeds 750 dynes seconds cm.[-5] exhibit either RVH or right ventricular conduction defect. It should be noted, however, that not all patients whose mean pulmonary arterial pressure exceeds 30 mm. Hg display electrocardiographic RVH. It has also been observed that those patients with chronic cor pulmonale who have hypoxemia (arterial oxygen saturation < 85 per cent) commonly show RVH in the electrocardiogram.

In conclusion, it may be stated that the electrocardiographic differentiation of cases of pulmonary emphysema without cor pulmonale from cases with cor pulmonale is often difficult or impossible. However, when the classic electrocardiographic pattern of RVH appears, it usually indicates advanced stages of the disease generally associated with pulmonary hypertension and hypoxia.

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REFERENCES

1. Zuckermann, R., Cabrera, E., Fishleder, B. L., and Sodi-Pallares, D.: Electrocardiogram in chronic cor pulmonale, Am. Heart J. 35:421, 1948.
2a. Wood, P.: Electrocardiographic appearances in acute and chronic pulmonary heart disease, Brit. Heart J. 10:87, 1948.
2b. Wood, P.: Diseases of the heart and circulation, ed. 2, Philadelphia, 1956, J. B. Lippincott Company.
3. Mounsey, J. P. D., Ritzman, L. W., and Selverstone, N. J.: Cardiographic studies in severe pulmonary emphysema, Brit. Heart J. 14:442, 1952.
4. Sodi-Pallares, D., and Calder, R. M.: New bases of electrocardiography, St. Louis, 1956, The C. V. Mosby Company.
5. Bremer, F. M., and Hellmuth, G. A.: The electrocardiographic diagnosis of chronic cor pulmonale, Tr. Am. Coll. Cardiol. 7:120, 1957.
6. Littmann, D.: The electrocardiographic findings in pulmonary emphysema, Am. J. Cardiol. 5:339, 1960.
7. Wasserburger, R. H., Kelly, J. R., Rasmussen, H. K., and Juhl, J. H.: The electrocardiographic pentalogy of pulmonary emphysema, Circulation 20:831, 1959.
8. Massie, E., and Walsh, T. J.: Clinical vectorcardiography and electrocardiography, Chicago, 1960, The Year Book Publishers, Inc.

9. Walsh T J Loman G T Jr and Massie F The ectoric ribographic QRS E loop findings in chronic cor pulmonale Am Heart J 60 592 1960
10. Grant R P Clinical electrocardiography The spatial vector approach New York 1957 Mc Graw Hill Book Company Inc
11. Phillips R W The electrocardiogram in cor pulmonale secondary to pulmonary emphysema study of 18 cases proved at autopsy Am Heart J 56 35 1958
12. Scott R C Kaplan S Fowler N O Helm R A Westcott R N Walker I C and Stiles W J The electrocardiographic pattern of right ventricular hypertrophy chronic cor pulmonale Circulation 11 927 1955
13. Spodick D H Electrocardiographic studies in pulmonary disease I Electrocardiographic abnormalities diffuse lung disease Circulation 20 1067 1960
14. M G B QRS-T patterns in multiple precordial leads that may be mistaken for myocardial infarction II Right ventricular hypertrophy and dilatation Circulation 1 950 1950
15. Corazza L J and P tor B H Cardiac arrhythmias in chronic cor pulmonale New England J Med 259 862 1958

Indicator-dilution techniques in diagnostic cardiology

Stewart first described the dilution principle for measuring blood flow which was subsequently applied to the study of the human circulation by Hamilton and his co-workers However the relatively recent work of Wood and his group[1] at the Mayo Clinic has stimulated great interest in the application of the indicator-dilution principle to diagnostic cardiology

The use of a great number of indicators has been described in a rapidly expanding literature Colored dyes (methylene blue Evans blue indigo carmine Coomassie blue and carboxyanine) radioactive liquids and gases (albumin I ethyl iodide I Kr) foreign gas (nitrous oxide) radiopaque dyes (Diodrast Hypaque C rd ograf) and radioisotope tagged red blood cells are some of the indicators which have been used in the study of circulation Although the technique and detecting devices may vary considerably depending on the indicator employed the principles underlying their use are common to all Thus experience gained with one indicator substance gives an understanding and permits evaluation of results obtained with others

Excepting the radiopaque dyes used in angiocardiography the practical choice of indicator lies among the colored dyes radioactive materials and foreign gases In our laboratory the colored dyes particularly carboxyanine have been used with considerable success The colored dyes yield results comparable to those obtained with radioisotopes they are inexpensive and their use obviates the need for maintaining a hot laboratory—an impracticability for most small institutions

To be sure not all colored dyes yield equally satisfactory results The introduction of carbocyanine by Fox and Coomassie blue by T for and Thorp has provided workers with dyes which do not stain the skin and which permit the recording of dilution curves not distorted by oxygen desaturation The chief disadvantage of dyes such as Evans blue has been eliminated

A good selection of detecting devices both of the earpiece and cuvette types is available In fact rugged reliable earpiece transducers can be expe assembled with easily obtainable material Such an earpiece has been in continuous use in our laboratory for over a year without breakdown

Perhaps the greatest diagnostic usefulness of indicator-dilution techniques is the detection and localization of central shunts Although routine cardiac catheterization and blood oxygen analyses will permit the detection of left-to-right and right-to-left shunts with the localization of left-to-right shunts a significant number of such shunts will remain undetected by this method False positives are also not uncommon Case and associates have pointed out the unreasonably small percentage increase in oxygen content (8 14 per cent) required for the diagnosis of left-to-right shunt by the oxygen method

As a rule moderate and large shunts in either direction or bidirectional shunts can be detected easily by application of indicator-dilution technique with much greater degree of accuracy than the conventional oxygen method Often simple inspection of the contour of dilution curves recorded from the ear after injection of indicator dye into peripheral vein or the vena cava suffices and serves as a useful screening procedure Exact localization of right-to-left shunt is accomplished easily with multiple injections of indicator upstream and downstream from the lesion

The localization of left-to-right shunts although more laborious can be accomplished by any of several satisfactory methods described in the literature These techniques involve either the use of two catheters in the right heart double lumen catheters or combined left and right heart catheterization

Approximate quantitation of the magnitude of a shunt is frequently possible by inspection of the recorded indicator-dilution curves More

qua titation may be achieved by measurement of the rious parameters of the dilution curve particularly when the per cent of shunted blood is sm ll

I telligent analysis and comparison of dilution curves recorded after the injection of ndicator i to arious locations in the heart and great essels allow the diagnosis of such lesions as anomalous pulmonary venous drainage aorticopulmonary win dow nd tran position of the great essels as well as other congenital nomalies

Indicator dil tion methods h e been pplied t the tudy of l ular disease particularly for the detection nd quantitation of regurgitant flow This pplication of the dilution principle because of technical and theoretical considerations has not been so successful m the study of central shunts Nevertheless useful pproximate quantita tion of regurgitant flow can usually be made and results obtained compare more fa orably with operati findings than do those obtained w th other ilable methods

One might question the need for diagnosing and lo lizing central shu ts so small that they are ndetected by the conventional oxygen method If the clinical findings however are such that diac catheterization is ndicated the fir t place then the use of ancillary methods which troduce no add tional hazard to the procedure nd llow mor accurate diagnosis is indicated It is not unlikely that many patients who were considered to have functional murmurs because of normal findings obtained during right heart catheter zation would be shown to have small septal defects or other anomalies if restudied with the aid of in licator dilution techniques The identification of such lesions and careful follow up would throw considerable light on the natural h tory of patients with shunt type defects and aid m clarifying the ndications for surgical intervention

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I EFFI RI NCI S

1 Stew irt G N Researches on the circul tion time in organs and on the influences which ffect t IV J Physiol 22 159 1897
2 Ham lton W F Moore J W K man J M and Spurling R C Simult neous determina tions of the pulmonary and systemic circulation times in man nd of a figure related to the car diac output Am J Physiol 84 338 1928
3 Nicholson J W III B rchell H B and Wood E H A method for the continuou re cord ng of E ns blue dye curves n rt ri l blood and its application to the diagnosis of cardiov scul bnormalities J Lab & Cl Med 3 353 1951
4 Fox I J Brooker L S G Heseltine D W Essex H F nd Wood E H A trie rbocy nine dye for continuous recording of dilution curves in whole blood independent of v ri tions in blood oxygen saturation Proc Staff Meet May Clin 32 478 1957
5 T ylor S H and Thorp J M Properties and biological beh ior of Cooma ie blue Brit Heart J 21 482 1959
6 Crump J (To be published)
7 Case R B Hurley H W nd Ke t k I Detection nd me urement of cir l tory sh ts by use of radio ct gas Prog Cardio as Dis 2 186 1959
8 Wiederhielm C A nd Bruc I A Diagnos s of tral shu ts from bnorm lities of peripher l dye dil tion curves AM HEART J 1 205 1957
9 Oakley C T ylor S Wikl D Hollm n A Good J F nd Shillingford J Dy dilution urves in congen tal he rt disease Brit Heart J 22 533 1960

Book reviews

DISEASES OF THE NEWBORN. By Alexander J. Schaffer, M.D., Associate Professor of Pediatrics, The Johns Hopkins Medical School and Pediatrician to the The Johns Hopkins Hospital, formerly Pediatrician-in-Chief and at present Attending Pediatrician at the Sinai Hospital of Baltimore, Md.; Chief of Pediatrics (Nursery Service), The Hospital for the Women of Maryland. Section on Neonatal Cardiology by Milton Markowitz, M.D., Assistant Professor of Pediatrics, The Johns Hopkins Medical School and Pediatrician to The Johns Hopkins Hospital, Attending Pediatrician and Director of the Division of Pediatric Cardiology, Sinai Hospital of Baltimore, Md. Philadelphia, 1960, W. B. Saunders Company. 878 pages. Price $20.

The section of this book written by Dr. Markowitz on disorders of the cardiovascular system of the newborn includes chapters on congenital heart disease, myocarditis, cardiac arrhythmias, miscellaneous conditions, and therapy. The introductory chapter contains a good assessment of fetal circulatory changes at birth and of manifestations of heart disease peculiar to the newborn. There is a pattern-type analysis of the electrocardiogram of the newborn without vector interpretations. The dissertations on myocarditis and arrhythmias will be particularly helpful to physicians concerned with the care of the newborn. Vascular anomalies involving the aortic arch are well presented with descriptive case histories of congenital stridor in the section on respiratory disorders. Persistent atelectasis in a 7-month-old infant without stridor was found to be caused by constriction of the left main bronchus between a patent ductus arteriosus and an aberrant left pulmonary artery.

Congenital heart disease has become a comprehensive subject and cannot be adequately considered in only the newborn phase of life. Thus this chapter deals with cardiovascular anomalies as they are encountered in early infancy and is of necessity abbreviated. A classification with regard to signs and symptoms is given as an aid to differential diagnosis. Emphasis is placed perhaps unduly on the anatomy of defects with frequent omission of the dynamic and functional effects of different anomalies on the pulmonary and systemic circulation. Catheterization data are not given, thus precluding graphic physiologic interpretations by the reader of clinical signs and radiographic and ECG changes caused by the different anomalies. Discussions of stenotic lesions involving the tricuspid, pulmonary, and aortic valves and transposition of the great vessels are especially appropriate and are well presented in this book. There is a good analysis with case histories of anomalous origin of a coronary artery from the pulmonary artery. However, there is no mention of the surgical treatment of this condition consisting of ligation of the vessel where it joins the pulmonary artery, a procedure proved to be rational by the demonstration of reversed blood flowing from the anomalous vessel to the pulmonary artery instead of the reverse type of flow so long presumed.

The liberal use of well-illustrated cases, several furnished to the authors by Dr. Helen Taussig of Baltimore, helps to make the cardiovascular section of this book interesting and useful to physicians concerned with diagnosis in infants.

CLINICAL VECTORCARDIOGRAPHY AND ELECTROCARDIOGRAPHY. By Edward Massie, A.B., M.D., F.A.C.P., F.A.C.C., Associate Professor of Clinical Medicine, Washington University School of Medicine, St. Louis, Mo.; Director of Heart Stations, Barnes Hospital and Jewish Hospital; Director, Cardiovascular Clinic, Washington University Clinics; Area Consultant in Cardiology, Veterans Administration; and Thomas J. Walsh, B.S., M.D., F.A.C.C., Instructor of Clinical Medicine, Washington University School of Medicine; Associate Director of Heart Station, Barnes Hospital; Visiting Physician, Jewish Hospital; Attending Physician, Washington University Service, Veterans Administration Hospital, St. Louis, Mo. Chicago, 1960, The Year Book Publishers, Inc. 592 pages. Price $27.50.

The stated purpose of this book is to bridge the gap between clinical electrocardiography, vector electrocardiography, and vectorcardiography, and as might be anticipated the book is encyclopedic in extent. The best features of the book are the many properly labeled and clear illustrations and the division of chapters into clinical syndromes such as cor pulmonale, congenital heart disease, mitral stenosis, and myocardial infarction, with summaries of the abnormal findings at the end of chapters. The chapters dealing with cardiac arrhythmias, drug and electrolyte disturbances, and the W-P-W syndrome are particularly well done.

There are several undesirable features of the book. The paragraphs describing vectorcardiograms are too verbose. This is caused by the difficulty of describing in print the complicated gyrations of vectorcardiograms. Verbal descriptions of electrocardiograms are awkward, but attempts to describe vectorcardiograms are hopelessly involved and tedious.

Another of the undesirable features concerns the first few chapters. In attempting to review new and basic matters the authors have got into deep water and consequently have made errors. Fortunately, most of these errors lead only to confusion on the part of the reader, but occasionally the paragraphs have a certain plausibility that could seriously mislead a newcomer to the field. The worst example of this occurs in Chapter 2, wherein Kirchhoff's law is badly misstated after being correctly stated a few pages earlier, and on both occasions has led the author to a wrong general conclusion which would be true only in a special

It regrettable th t the uthors h dropped the newer oncept of some exchang because f it omplexit in fa or of the old Bernstein meml ane theory nce the ne er idea partic ular l onnection with membrane potential tudies h provided much information in regard t the action f drugs planation of injury current nd the effect of electrolytes Fortunately ev rything the thor ha written ng Bern tein theory is equally pplicable or more so nder the newer ideas so that no serious errors ha been made result

La tly the revie er deplores the use of non rthog nal lead tem t record ectorcardio-grams Although t is true th t ll ectorcardio grams are interpreted empirically in some degree this pproach w ll only conf se future studies based on lead ystems that re more truly orthogonal It must be remembered that er torcardiograms will be truly in the frontal horizont l and sagittal planes only if good orthogonal lead are employed

Lest it seem that the reviewer is overcritical it might be poi ted out that the serious objections to the book pply to small fraction of it and actually there i much acc rat and usef l information particularly on onvent onal elec trocardiography in the book

Announcements

THE LIFE I SU CE MEDICAL RE EA RCH FU D is now recei ing pplicat ons for two types of ward to be ailable July 1 1962 as follow (1) *Until Oct 1 1961* for postdoctoral research fellow h ps Candida es ma pply for pport in y field of he medical sciences Preference given t those ho h t work on fundamental problem especiall those related t card va scula funct on or disease Minimum tipened is $4 500 with all ances for dependent and necessary tra l (2) *Until Nov 1 1961* for grants to institutions in aid f research on ardio scular problems Support is ailable for ph logical biochemical and other ba ic work broadl related t cardiovascular problem as well as for linical research in this field

Further formation and application forms ma be obtained from the Scientific Director Lif I urance Medical Research F nd 1030 East Lanca ter A Rosemo t Pa

The Staff of the Department of Radiology t the Univer ty of Rochester regret that it was not pos ible to hold the THIRD SYMPOSIUM ON CINE FLUOROGRAPHY the Spring of 1961 as originall announced I tead the meeting will be held in Rochester New York on Frida and Saturda Dec 1 and 2 1961 As before the seating capacity of the auditorium will limit *regi tratio* t approximately 150 ndiv duals

The program will include ba ic entat in problems of motion picture radiography as well demon trations of the applications of cinefluor ography in the basic sciences and cl nical sciences

This announcement is an invitation for the submission of scientific papers dealing with any facet of the technical or pplied pect of motion pict re radiography

Address inquiries or pplications t Sta ley M Rogoff M D Di on of Diagnostic Radiology University of Rochester Medical Ce ter Rochester 20 N Y

THE FOURTH WORLD CONGRESS OF CARDIOLOGY ill be held from O t 7 through 13 1962

The ses ons will be hel t the Congress Build ng which was recently built t the Medical Center in Mexico Cit The Congress Building is only few steps from the Instituto Nacional de Cardiol gia nd ha the best facil ties for both scientific sessions and technical exhibit

THE COUNCIL ON POSTGRADUATE MEDICAL EDUCA TION OF THE AMERICAN COLLEGE OF CHEST PHY SICIA S will present the following postgraduate courses during 1961 *Cardiopulmonary Problems in Children* Brow Hotel Denver Colo July 24 28 *Industrial Chest Diseases* Warwick Hotel Phila delphia I Sept 25 29 *Clinical Cardiopulmonary Physiology* Sheraton Chicago Hot l Chica Ill Oct 23 27 *Recent Advances in the Diagnosis nd Treatment of Heart nd Lung Diseases* Park Sheraton Hotel New York N Y Nov 13 17 *Recent Advances in Diseases of the Chest* St tler Hilton Hotel Los Angeles Calif Dec 4 8

Further information may be obtained by riting the Executiv Director America College of Chest Physicians 112 East Chestnut Street Chicago 11 Ill

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